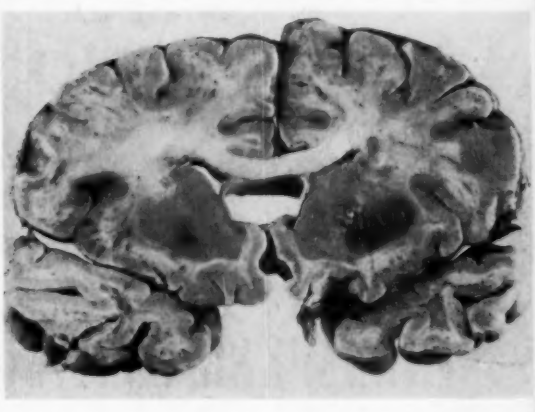
A.M.A.

Archives OF NEUROLOGY AND PSYCHIATRY

FEBRUARY 1956

VOLUME 75 NUMBER 2

From Boshes et al., p. 175



AMERICAN MEDICAL ASSOCIATION Publication

COLONIAL HALL
One of Fourteen units in "Cottage Plan"

For Nervous Disorders

Maintaining the highest standards since 1884, the Milwaukee Sanitarium Foundation continues to stand for all that is best in the contemporary care and treatment of nervous disorders.

Photographs and particulars sent on request.

Josef A. Kindwall, M.D.
Carroll W. Osgood, M.D.
William T. Kradwell, M.D.
Benjamin A. Ruskin, M.D.
Lewis Danziger, M.D.
Russell C. Morrison, M.D.
James A. Alston, M.D.
Ellis Bonnell, M.D.

★

Waldo W. Buss, Executive Director

Chicago Office—1509 Marshall Field Annex Bldg.
25 East Washington St.—Wednesday, 1-3 P.M.
Phone—Central 6-1162

MILWAUKEE SANITARIUM FOUNDATION, INC.

Wauwatosa • Wisconsin

TABLE OF CONTENTS

VOLUME 75 FEBRUARY 1956 NUMBER 2

ORIGINAL ARTICLES

SPECIAL ARTICLES

REGULAR DEPARTMENTS

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 75 FEBRUARY 1956 NUMBER 2

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $14.00

INDEX TO

NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA

Advertising in

A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an every-other month basis it would be necessary to consult the advertising section of a previous or *subsequent issue.*

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. A carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given. To avert the possibility of legal action, patients' initials and hospital case numbers should not be published.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. See an issue of this journal for examples. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins (or mountings) rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

STRIKING RESULTS OBTAINED WITH "MYSOLINE" IN GRAND MAL SEIZURES AND PSYCHOMOTOR ATTACKS.

Composite results of 20 clinical studies* show that "Mysoline" employed alone or in combination with other anticonvulsants is highly effective in controlling epileptic seizures.

In patients previously untreated "Mysoline" employed alone produced complete control of grand mal seizures in 172 of a total of 214 patients (80 per cent); psychomotor attacks were brought under control in 19 of 29 (65 per cent).

In patients refractory to other anticonvulsants "Mysoline" produced marked improvement to complete control of grand mal seizures in 428 of 613 patients (nearly 70 per cent). In the group with psychomotor attacks a similar response was obtained in 75 of 130 patients (over 57 per cent). "Mysoline" was added to current medication and in some cases this was replaced by "Mysoline" alone.

"Mysoline" is singularly free from serious toxic effects.

Side effects when they occur are usually mild and transient tending to disappear as therapy is continued or dosage is adjusted. Supplied in 0.25 Gm. tablets (scored) — bottles of 100 and 1,000.

*References will be supplied on request.

"MYSOLINE"®

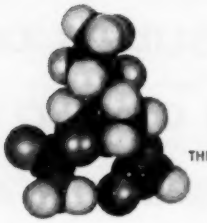
Brand of Primidone

IN EPILEPSY

Ayerst Laboratories • New York, N.Y. • Montreal, Canada

Ayerst Laboratories make "Mysoline" available in the United States by arrangement with Imperial Chemical (Pharmaceuticals) Limited.

5558



THE MILTOWN MOLECULE

Two articles in the April 30th issue of The Journal of the AMA[1,2] report on . . .

an entirely new type of tranquilizer with muscle relaxant action—orally effective in

ANXIETY, TENSION and MENTAL STRESS

- no autonomic side effects—well tolerated
- selectively affects the thalamus
- not related to reserpine or other tranquilizers
- not habit forming, effective within 30 minutes for a period of 6 hours
- supplied in 400 mg. tablets. Usual dose: 1 or 2 tablets—3 times a day

1. Selling, L. S.: J.A.M.A. **157:** 1594, 1955. 2. Borrus, J. C.: J.A.M.A. **157:** 1596, 1955.

Miltown®

the original meprobamate—2-methyl-2-n-propyl-1,3-propanediol dicarbamate—U. S. Patent 2,724,720

DISCOVERED AND INTRODUCED by Wallace Laboratories, New Brunswick, N. J.

Literature and Samples Available On Request

A.M.A. Archives OF NEUROLOGY & PSYCHIATRY

Effect of Isoniazid in Multiple Sclerosis with Chronic Symptomatology

L. P. HINTERBUCHNER, M.D.
M. G. GOLDNER, M.D.
J. B. ROGOFF, M.D.
and
A. M. RABINER, M.D., Brooklyn

Multiple sclerosis is a disease characterized by remissions and exacerbations of symptoms. Thus, any considerations of therapeutic influences on the symptomatology must be subjected to critical analysis because of the natural fluctuations in the course of the disease. Recently isoniazid was reported as favorably influencing multiple sclerosis. In their preliminary report, Kurtzke and Berlin [1] did not claim unequivocal effectiveness of isoniazid but suggested that their results warranted further investigation. Their patients were, in the main, persons who had recent exacerbations of rather short duration.

This communication presents the results of the use of isoniazid in patients with multiple sclerosis of long standing. It was felt that a study of the effect of the drug on patients with persistent disabling features of the disease would be of special value for the evaluation of its therapeutic efficacy. In addition, a group of patients with other neurological disorders was selected for the purpose of studying the specificity of a possible effect of isoniazid. If no such specificity could be demonstrated, it was hoped that some clue as to the mode of its influence on neurological diseases could be obtained.

Received for publication Oct. 24, 1955.

From the Departments of Neurology, Medicine, and Physical Medicine and Rehabilitation of the Jewish Chronic Disease Hospital.

METHODS AND MATERIAL

Twenty-eight patients with multiple sclerosis of long standing and 12 patients with other chronic neurological disorders were selected from the population of the Jewish Chronic Disease Hospital in Brooklyn. The diagnosis of multiple sclerosis was considered to be established when the following criteria were fulfilled:

1. Symptomatology related to more than one localization in the nervous system
2. History of remissions and exacerbations
3. No specific etiological agent demonstrable

Moreover, many of the patients in this series had been studied in other neurological clinics with no

TABLE 1.—*Data on Patients with Multiple Sclerosis and Patients with Other Neurological Disorders* *

	Multiple Sclerosis		Other Neurological Disorders	
	Average	Range	Average	Range
Total no.	25		10	
Age	46	24-62	52	45-68
Age on admission	41	23-59	43	24-65
Age at onset of disease	25	7-47	30	17-48
Duration of illness	20	6-47	21	3-37
Age at time of last remission	26†	15-48†	‡	‡
Years since last remission	18	6-47	‡	‡

* All data expressed in years.
† Average for 20 patients with recorded remissions.
‡ Two patients of the group with other neurological disorders, both with a history of encephalitis followed by demyelinating syndrome, had remissions—one three years after onset, at the age of 20, or 25 years ago; the other shortly after the onset at the age of 18, or 22 years ago.

disagreement as to the diagnosis, despite the fact that five patients of this group had no demonstrable remissions. Protein studies of the blood and spinal fluid, which had been carried out on the majority of these patients prior to this investigation, conformed to the "protein profile" of multiple sclerosis, as described by Volk and associates.[2] The group of 12 patients with neurological disorders other than multiple sclerosis included 4 patients with postencephalitic Parkinsonism, 3 with postencephalitic demyelinating syndrome, 2 with syringomyelia, 2 with amyotrophic lateral sclerosis, and 1 with a post-traumatic demyelinating syndrome. The vital statistics of both groups in terms of their respective average and range of age, age on admission at the onset of disease, duration of illness, age at the time of last remission, and years since last remission are given in Table 1. Individual data are shown in Tables 3 and 4, together with the results of the study. It will be noted that these Tables present data on only 25 patients with multiple sclerosis and 10 patients with other neurological disorders. Three patients with multiple sclerosis and two with other disorders were eliminated from the series because of their refusal to continue medication. They will be discussed separately.

In the study, the double blind method of drug administration with placebo was employed. Neither the examiners nor the patients knew whether the medication used in any particular case was isoniazid or placebo. The dispensing of medication, identified by number only, was carried out by one member of the team, who at no time during the study came in contact with the patients, or even their names. After the initial examination the patients were started on 3 capsules of the medication daily and the treatment continued for about three months. Capsules (100 mg.) of isoniazid and capsules of placebo of identical size, appearance, and taste were used.*

All patients were given complete physical examinations prior to the study and at weekly intervals thereafter. In addition, at the beginning and at six-week intervals the following tests were carried out:

1. A Manual Muscle Test, evaluating the power in all muscle groups of the extremities, was done. The results of this testing were expressed in percentages, or equivalents in grades, as recommended by the National Foundation for Infantile Paralysis. An improvement of 25% or a "full grade" for the whole limb was considered significant.

Thus, for instance, in Patient 20 the following changes took place between the initial and the final examination in the muscles of the right shoulder girdle:

Flexors: Fair-plus to good-plus, equivalent to +25%, or +3/3 grade
Extensors: Fair-plus to good, equivalent to +15%, or +2/3 grade
Abductors: Fair-plus to good-minus, equivalent to +5%, or +1/3 grade
Horizontal abductors: Fair-plus to good-plus, equivalent to +25%, or +3/3 grade
Horizontal adductors: Fair-plus to good-plus, equivalent to +25%, or +3/3 grade
External rotators: Fair to fair, no change
Internal rotators: Fair to fair, no change
Average for shoulder: +13%, or 0.57 grade.

Similarly, averages for other parts of the limb were calculated:

Elbow: +20%, or +2/3 grade
Forearm: +25%, or +3/3 grade
Wrist: +10%, or +1/3 grade
Fingers: +20%, or +2/3 grade
Thumb: +14%, or +1.4/3 grade

From these a total average for the whole extremity was calculated. In this case it was +17%, or an improvement of about 0.6 grade.

2. Measurements of range of active motion at all joints. These were expressed in percentages of expected normal.

Thus a 0- to 165-degree range of active abduction in the shoulder joint, expressed in per cents of expected normal range (0 to 180 degrees) is about 90% of the normal. If a range of 0 to 170 degrees, which is equivalent to about 95% of normal, was obtained at the next testing, the increase was equal to the difference between the first and final measurement. These measurements were obtained for flexion, extension, and medial and lateral rotation of the shoulder joint, in addition to the already mentioned abduction. An average was then calculated for shoulder joint, and eventually for the whole limb.

3. Activities of Daily Living (ADL). Each patient was tested for 154 daily activities. The performances were expressed in five grades in accordance with the modified ADL Forms of the Veterans Administration. No simple numerical expression of changes was practicable. Therefore, all the 154 tested Activities of Daily Living were judged on their individual merits.

The results of the follow-up examinations were carefully recorded, and at the end of the study evaluated by the team of examiners. The decoding of the drug numbers was performed only after recording of the evaluations of the results.

*Dr. Elmer L. Sevringhaus, of Hoffmann-La Roche, Inc., Nutley, N. J., supplied us with the drug and made many helpful suggestions.

RESULTS

Of the total of 40 patients, 35 tolerated the medication without subjective or objective untoward effects, while 5, as stated above, refused to continue the medication.

Of these five patients, only one had been receiving isoniazid; the other four had placebo. Isoniazid was refused by a patient with postencephalitic Parkinsonism after six days of medication. No untoward signs or symptoms were observed or claimed. Two patients with multiple sclerosis refused to continue the medication after four and eight days, respectively. One of them complained of blurred vision, dizziness, and lack of improvement; the other, of diplopia, dizziness, generalized weakness, nausea, and vomiting, all of which subsided promptly after the medication was discontinued. At the time of decoding, some three months later, it was revealed that these patients had been receiving placebos. The two remaining patients, one with multiple sclerosis and the other with amyotrophic lateral sclerosis, received medication for 29 and 77 days, respectively, with several interruptions, and refused to continue because of increased generalized weakness and increased spasticity, respectively. Objective examination showed that the general condition of both these patients had remained about the same. They, too, had been receiving placebo.

All the remaining 35 patients received uninterrupted treatment for a minimum of 85 days, except for 5 patients (Nos. 32, 38, 39, 40, and 17). Of these, two patients (Nos. 32 and 38), both with multiple sclerosis, received isoniazid for 78 and 79 days, respectively. The remaining three patients (Nos. 39, 40, and 17) received placebo for 72, 81, and 62 days, respectively. The group on isoniazid and the group on placebo were comparable in terms of their range and average of age, age on admission, age at the onset of the disease, duration of illness, age at the time of last remission, and years since last remission, as shown in Table 2.

Isoniazid.—Multiple Sclerosis Group: Of the 11 patients with multiple sclerosis treated with isoniazid, some improvement appeared in 4 (Nos. 3, 13, 18, and 32, in Table 3), but this was in none of them of more than minimal significance. None of the patients in this group regarded themselves as improved during the study, but two reported that they were more relaxed. Two patients complained of increased weakness.

Group with Other Neurological Diseases: Of the six patients in this group, some improvement was recorded in two (Nos. 26 and 27, in Table 3), in neither of whom could it be considered significant. The continued downhill course of a patient with amyotrophic lateral sclerosis (No. 35) appeared in no way influenced by the medication. Two patients (Nos. 2 and 27) felt more relaxed during the study. A patient with postencephalitic Parkinsonism (No. 26) complained of increased tremor.

Placebo.—Multiple Sclerosis Group: As summarized in Table 4, of the 14 patients

TABLE 2.—*Vital Statistics on Group Receiving Isoniazid and Group Receiving Placebo* *

	Multiple Sclerosis				Other Neurological Diseases			
	Isoniazid		Placebo		Isoniazid		Placebo	
	Average	Range	Average	Range	Average	Range	Average	Range
Total no.	11		14		6		4	
Age	45	31-60	47	24-62	48	45-54	55	44-68
Age on admission	39	28-52	43	23-59	45	27-50	41	24-51
Age at onset of disease	25	18-42	26	7-47	40†	17-48†	32	17-38
Duration of illness	18	12-34	22	6-47	21†	3-37†	22	13-27
Age at time of last remission	28	20-48	15	16-41	‡	‡	‡	‡
Years since last remission	15	6-32	14	8-47	‡	‡	‡	‡

* All data expressed in years.
† This figure includes a patient with amyotrophic lateral sclerosis beginning three years ago, at the age of 48. When calculated without him, the average age of onset reads 22 instead of 40 years, and the average duration of illness, 25 instead of 21 years.
‡ See corresponding footnote in Table 1.

TABLE 3.—*Data on Patients on Isoniazid*

Case No.	Sex	Age	Age at Onset	Age at Last Remission	Kurtzke's Class	Days on Isoniazid	Diagnosis	Power*	Range*	ADL	Objective Neurological	Subjective Claims
1	F	44	26	28	8	129	Multiple sclerosis	0	0	0	0	Weaker
3	F	59	31	28	9	105	Multiple sclerosis	0	+2.2% LU	0	0	0
4	F	36	18	21	9	105	Multiple sclerosis	0	0	0	0	Generalized weakness; malaise 1 mo. later
9	F	40	27	26	9	88	Multiple sclerosis	0	0	0	0	More relaxed 10 days after start
10	M	35	23	24	9	103	Multiple sclerosis	0	Flicker of mov. right finger	0	0	0
13	M	47	31	32	8	126	Multiple sclerosis	+18% LU +23% RU	+19% LU	Minimal improvement	0	Relaxed, hazy vision, general weakness
18	F	60	42	48	9	123	Multiple sclerosis	+11% LU + 4% RU	0	Mildly worse	0	0
19	F	31	19	20	9	98	Multiple sclerosis	0	0	0	0	0
26	F	53	25	41	9	117	Multiple sclerosis	0	0	0	0	0
32	M	42	21	36	9	78	Multiple sclerosis	+5.4% RU	+15% RU	0	0	Felt better after discontinuation of drug
38	F	34	22	23	9	79	Multiple sclerosis	0	0	0	0	0
2	F	54	17	..	8	147	Postencephalitic Parkinsonism	0	0	0	0	More relaxed 1st month of therapy
26	F	47	19	..	5	113	Postencephalitic Parkinsonism	0	+1.2% LU + 3% LL	0	0	Shakes more
27	F	50	19	..	9	110	Postencephalitic demyelinating syndrome	0	+2.2% LU + 11% RU	Worse	0	10 days: more relaxed, then weaker
29	F	45	26	..	8	104	Postencephalitic Parkinsonism	0	0	0	0	0
30	F	50	18	8	6	101	Postencephalitic demyelinating syndrome	0	0	0	Decreased spasticity in right extremities	0
35	M	51	48	..	9	85	Amyotrophic lateral sclerosis	−20% LL −14% RL − 2% LU −10% RU	−34% RL − 3% LL	Worse	Same findings more pronounced	Worse

* RU indicates right upper extremity; LU, left upper extremity; RL, right lower extremity; LL, left lower extremity.

TABLE 4.—*Data on Patients on Placebo*

Case No.	Sex	Age	Age at Onset	Age at Last Remission	Kurtzke's Class	Days on Placebo	Diagnosis	Power	Range of Active Motion	ADL	Objective Neurologic Improvement	Subjective Claims
5	F	60	37	41	8	140	Multiple sclerosis	+14% LU +19% RU	0	Worse	0	Could unbutton jacket; increased incontinence
6	F	62	15	15	8	126	Multiple sclerosis	0	0	0	0	15 days after onset blurred vision
8	F	53	33	36	9	119	Multiple sclerosis	0	0	0	0	Transient retention of urine
11	M	39	14	21	8	97	Multiple sclerosis	+6% LU +6% RU	0	0	0	Increased spasticity; increased weakness
12	M	44	34	..	8	101	Multiple sclerosis	0	0	0	0	Transient decrease of spasticity
15	M	24	14	16	8	98	Multiple sclerosis	+20% LU +20% RU	+2% LU +1% RU	Better	Decreased ataxia; decreased urinary freq., decreased spasms	50% decrease of spasms in 2 days; decreased urinary freq.; less incoordination
16	F	44	32	32½	8	100	Multiple sclerosis	0	0	0	0	0
20	M	48	29	30	6	94	Multiple sclerosis	+25% LU +17% RU	+1% RU	0	0	Increased spasticity and weakness
21	M	44	23	..	9	105	Multiple sclerosis	0	0	0	0	0
22	M	43	7	20	6	92	Multiple sclerosis	0	+1.5% RU	0	0	0
36	F	38	24	..	8	95	Multiple sclerosis	+ 8% LU +10% RU	0	0	0	0
37	F	59	40	..	8	90	Multiple sclerosis	0	+1% RU	Improv. in writing	Increased range of motion at 3d week	This disappeared in the fifth week; decreased vision; increased weakness
39	F	58	47	..	8	72	Multiple sclerosis	0	0	0	0	0
40	F	51	9	20	9	81	Multiple sclerosis	+4% LU	0	0	0	0
17	F	44	24	20	9	64	Postencephalitic demyelinating syndrome	0	0	Improvement	0	Able to feed self 2 days after start
24	F	40	36	..	9	111	Post-traumatic demyelinating syndrome	0	0	Worse	0	0
28	M	60	38	..	9	108	Syringomyelia	0	0	0	0	0
33	M	68	42	..	9	89	Syringomyelia	+11% LU +19% RU − 7% LL + 9% RL	+3% LU +15% RU + 1% RL	0	0	Weaker

with multiple sclerosis receiving placebo, 6 showed improvement (Nos. 5, 11, 15, 20, 36, and 40). In only three (Nos. 5, 15, and 20) could this improvement be considered of any significance. Only one (No. 15) was aware of the improvement, which appeared on the third day of the study, was evident in all objective examinations, and remained throughout the study and after its completion. Marked improvement in muscle power appeared in Patient 20, in whom a full-grade improvement took place in the left upper extremity. The patient, however, complained of increased spasticity and weakness. Four other patients of this group claimed to have transient impairment of various faculties (Nos. 5, 6, 8, and 11). One (No. 37) showed a transient improvement in range of active motion of the upper extremity, which was discovered at the weekly neurological examination and was followed by a relapse. One patient (No. 12) had transient diminution of spasticity of very short duration.

Group with Other Neurological Diseases: One of the four patients in this group (No. 17) showed improvement in Activities of Daily Living of such a degree that some regression of severe cerebellar symptomatology was postulated. The patient who had been unable to feed herself could now do so. Mild improvement in muscular power occurred in Patient 33.

COMMENT

Method.—In discussing the methods of the testing employed in this study, and especially the attempt to express results numerically, we were well aware of the inadequacies and sources of error in calculations. To be more specific, it was quite apparent that an improvement in muscle power from a "fair-plus" to "good-minus," expressed as "+5% improvement" (the normal being 100% and the trace 10%), was not the same when expressed in terms of grades as improvement by 1/3 grade. However, both ways of calculations were carried out in most of the patients, and the differences in final results proved to be extremely minimal. This is well illustrated by the example of such calculation as that shown above in the description of methods. Thus, either way can be used, as differences do not reach an order of magnitude considered significant, namely, a full-grade, or 25%, change. As for the range of active motion, we felt that our numerical calculations were adequately close to the true state of the patient's function.

The Activities of Daily Living defied any attempt to express changes in a numerically significant way. One cannot well compare 2-grade improvement in the ability to turn on a faucet with 2-grade improvement of getting into bed. However, each of the 154 points is significant when considered against the background of the total functional capacity of the patient. Thus, we chose to evaluate all the changes in Activities of Daily Living on their individual merits pertinent to the particular patient under consideration.

The tests described were carried out by the same examiners in order to lessen the possibility of error based on different techniques.

Results.—As is apparent from Tables 3 and 4, summarizing the results of this study, changes occurred in all groups regardless of whether isoniazid or placebo was administered. It is noteworthy that the only significant improvement comparable to that reported by Kurtzke and Berlin occurred in a patient (No. 15) receiving placebo. It should be mentioned that this is one of the youngest patients of our series with respect both to age and to the duration of the disease. His initial symptoms occurred about 10 years ago, and he became seriously disabled five years ago. Several weeks after discontinuation of placebo the improvement was no longer noticeable. This obviously represents a remission, such as occurs so often in multiple sclerosis.

Of the group of 17 who received isoniazid, 4 (Nos. 9, 13, 2, and 27) reported that they felt relaxed during the study, and 3 reported what was considered to be an equivalent of relaxation. Thus, two patients with spasticity (Nos. 1 and 4) reported increased weakness, and one patient with extrapyramidal rigidity

(No. 26) complained of increased tremor. Of these seven patients, four had multiple sclerosis, two had postencephalitic Parkinsonism, and one had a postencephalitic demyelinating syndrome. No similar reports were obtained from patients receiving placebo; i. e., none specifically reported a feeling of relaxation, and those complaining of increased weakness were in general not as definite, specific, or consistent in their statements as the group receiving isoniazid.

It seems justifiable to conclude from these observations that isoniazid does not favorably influence the course of patients who have had multiple sclerosis for a long period.

As stated above, a sense of "relaxation" was reported by some of the patients on isoniazid. This occurred both in patients with multiple sclerosis and in those with other neurological disorders. The significance of this finding is open to speculation.

It is of interest that, although isoniazid has been reported as an etiological factor in peripheral neuropathy,[3] no evidence of such was found in any of the patients under the present study.

SUMMARY

Of 25 patients with multiple sclerosis of long standing, 11 were given isoniazid and 14 placebo. Likewise, 6 of a group of 10 patients with other chronic neurological disorders received isoniazid and 4 placebo.

Improvement, though only of minimal to moderate significance, occurred in only three patients with multiple sclerosis. These three were receiving placebo. In all other groups minimal changes occurred. These evidently were independent of the medications given.

Isoniazid does not seem to influence favorably the course of patients who have had multiple sclerosis for a prolonged period of time.

Dr. O. Miglietta, Resident in Neurology; Mr. Murray Crystal, Chief Physical Therapist, and Mrs. Joan Holder, Chief Occupational Therapist, assisted in this study.

ADDENDUM

Our results are in agreement with the findings of M. C. Korengold and associates, of the National Institute of Neurological Diseases and Blindness, Bethesda, Md. (*Neurology* **5**:801, 1955), which appeared after this manuscript was submitted for publication.

REFERENCES

1. Kurtzke, J. F., and Berlin, L.: The Effects of Isoniazid on Patients with Multiple Sclerosis, Am. Rev. Tuberc. **70**:577-592, 1954.

2. Volk, B. W.; Saifer, A.; Rabiner, A. M., and Oreskes, I.: "Protein Profile" in Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. **73**:66-75, 1955.

3. Hughes, H. E.; Biehl, J. P.; Jones, A. P., and Schmidt, L. H.: Metabolism of Isoniazid in Man as Related to the Occurrence of Peripheral Neuritis, Am. Rev. Tuberc. **70**:266-273, 1954.

Electrophysiological Analysis of Psychotogenic Drug Action

I. Effect of LSD on Specific Afferent Systems in the Cat

DOMINICK P. PURPURA, M.D., New York
With the Technical Assistance of Desmond Callan, A.B.

The clinical effects of agents which produce transient toxic psychotic behavior in man have been described and studied intensively.* Recently biochemical alterations similar to those described in chronic schizophrenics have been produced following the administration of one of these agents LSD.† The structural similarity of certain psychotogenic agents to various degradation products of epinephrine also reported to be psychotogenic ‡ has given impetus to the concept, not new,[8] that the so-called functional psychoses result from endogenous metabolic disturbances. It is beyond the scope of this paper to evaluate the validity of this hypothesis.

To the neurophysiologist the psychotogenic agents offer a special challenge. The biophysical symbols of chemical events which are studied may provide some clues as to the possible mechanism by which these drugs alter the functional activity of the brain. In this and in the subsequent paper investigations of the effects of LSD on the evoked electrocortical activity of the cat's brain are

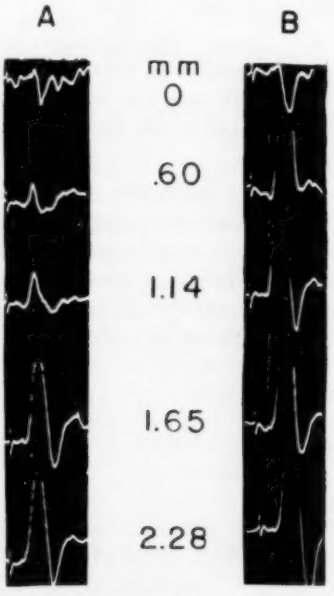


Fig. 1.—Laminar responses recorded in auditory cortex following click stimulation to contralateral ear. Unanesthetized-paralyzed animal.

A, control responses from various depths recorded three hours after termination of ether anesthesia. Microelectrode approximately 10μ tip diameter.

B, facilitated auditory responses five minutes after 40γ/kg. of LSD, I.V. In this, and in all subsequent records, negativity at the recording electrode is signaled by an upward deflection.

Received for publication Aug. 2, 1955.

Special Research Fellow, National Institute of Neurological Diseases and Blindness, U. S. Public Health Service.

Presented in part at the 80th Annual Meeting of the American Neurological Association, Chicago, June 13, 1955.

From the Laboratory of the Department of Neurological Surgery, Columbia University College of Physicians and Surgeons.

* References 1 to 4.

† Reference 5. Throughout these communications LSD will refer to *d*-lysergic acid diethylamide-25, which was supplied by Sandoz Pharmaceuticals, Division of Sandoz Chemical Works, Inc., Hanover, N. J.

‡ References 5 to 7.

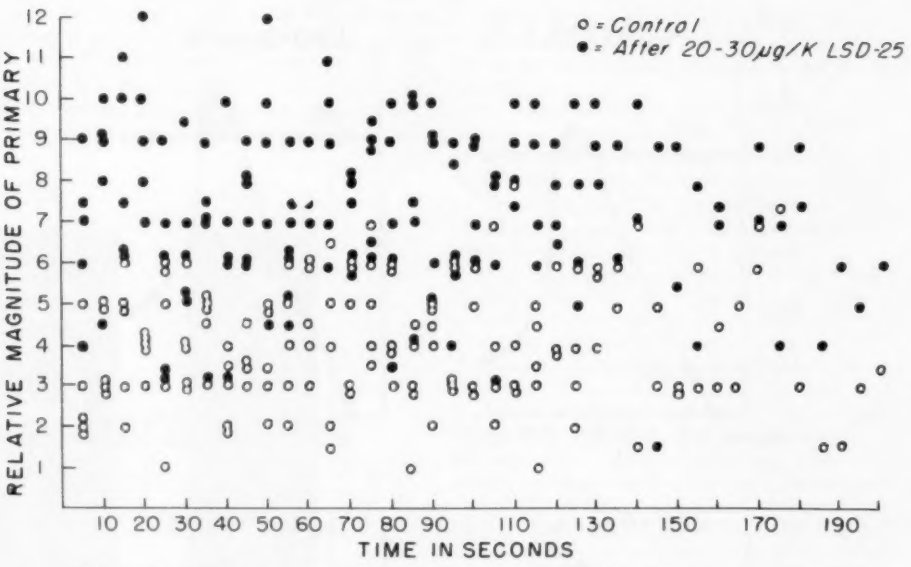


Fig. 2.—Facilitation of auditory primary responses; composite of five experiments. Two animals initially prepared with ether anesthesia, three with light barbiturization, and the animals permitted to recover. Click stimuli were delivered every 5 seconds for as long as 200 seconds in one instance. Note marked variability of responses in control state and general elevation of responses after LSD.

presented in an attempt to elucidate the electrophysiological concomitants of the psychotogenic drug action.

METHODS

The selective inhibition by barbiturates of the complex interneuronal activity of the neuraxis § necessitated abandonment of these agents in neuropharmacological studies with drugs which presumably disorganize the perceptual and integrative activity of the brain. For this reason experiments were performed as follows:

Forty-three adult cats (2.5-5.0 kg.) were utilized in acute experiments reported in this and in the subsequent paper. Thirty animals were initially anesthetized with either pentobarbital sodium (35 mg/kg.) or ether. At the completion of the operative work all skin margins and pressure points were infiltrated with procaine and the animals were permitted to recover. Immediately after termination of the ether anesthesia, and within a few hours after the light barbiturization, the animals were paralyzed by means of a succinylcholine chloride-saline infusion and placed on artificial respiration. They could be maintained in excellent condition in this manner for many hours without evidence of deterioration. Preliminary experiments with massive doses of succinylcholine failed to demonstrate any effects on electrocortical activity that could be attributed to the neuromuscular relaxant. The total volume of infusion was kept below 20 cc/kg. Urinary output was excellent and was considered a reflection of the excellent cardiovascular state of the

§ References 9 and 10.

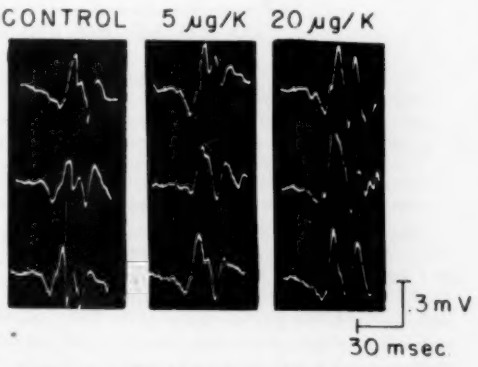


Fig. 3.—LSD facilitation of visual primary responses to flash stimulation of the contralateral retina (pupil dilated with atropine). Note especially potentiation of the responses following the initial surface positive-negative sequence constituting the primary response.

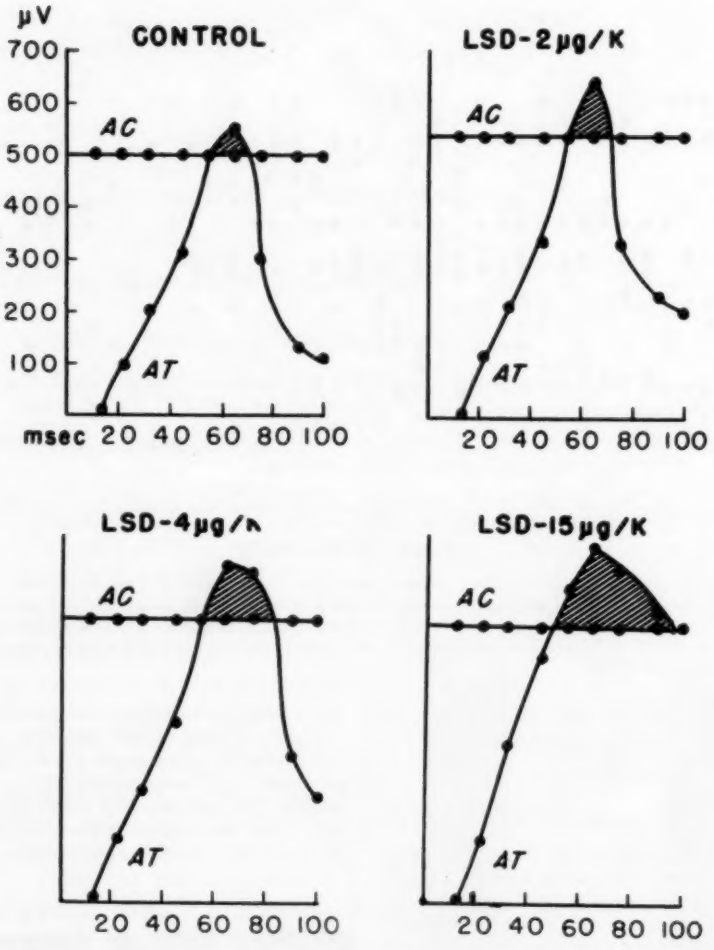


Fig. 4.—*AC*, auditory "conditioning" response; *AT*, auditory "testing" response. Alteration in the recovery cycle of excitability of the auditory primary system with graded doses of LSD. Control records from which curves were plotted were obtained eight hours after initial barbiturization and five hours after continuous succinylcholine paralysis. Note that after 2γ/kg. of LSD significant alteration occurs in the recovery cycle of the auditory primary response. This becomes more impressive after an additional 4γ/kg., and then 15γ/kg. Shaded area in each instance represents time course of supernormal excitability following the initial "conditioning" response.

preparations. A control period of from 30 minutes to 1 hour, beginning two hours or more after the start of the succinylcholine drip, was usually employed prior to the administration of the LSD. No animal was utilized in this series whose spontaneous electrocortical pattern revealed high-voltage spindle activity. Although the relationship between electrical pattern and level of "awareness" has been challenged on clinical grounds,‖ a continuous pattern of low-voltage high-frequency activity was considered significant electrical evidence for the absence of residual anesthesia in the paralyzed animals.

In 13 animals the initial dose of pentobarbital sodium was supplemented by repeated small doses, given intravenously, to maintain the animals at a moderately deep level of narcosis.

The cortical potentials studied in this report were evoked in the auditory, visual, or somesthetic cortex after a click, flash (35 μsec.), or sciatic nerve

‖ References 11 and 12.

stimulation. The usual precautions were observed to prevent drying or cooling of the cortex during the long procedures. In all instances the dura remained intact until complete recovery from initial anesthetization. Cortical potentials were recorded monopolarly in most instances with silver ball electrodes placed with three-dimensional micromanipulators and maintained in the same position throughout the experiment to avoid potential changes attendant upon areal displacements. The indifferent electrode consisted of a steel screw embedded in the calvaria over the frontal sinus. In a few experiments two microelectrodes of 10μ tip diameter with a vertical displacement of 1 mm. were placed to record at superficial and deep levels, respectively, of the auditory cortex without movement during the experiment.

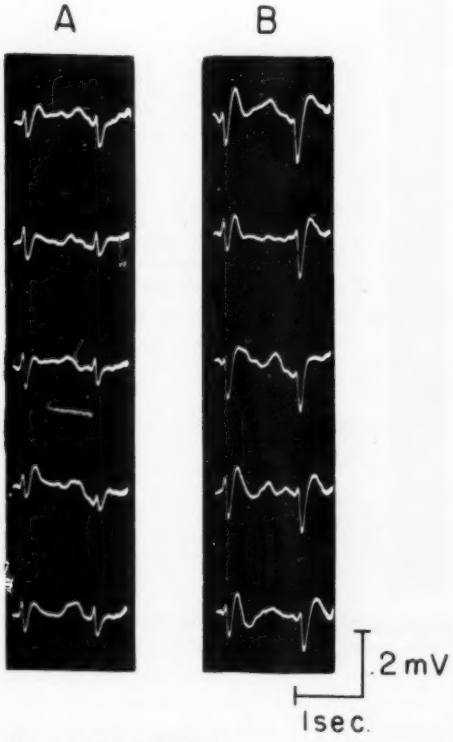


Fig. 5.—*A*, control; *B*, two minutes after LSD 25γ/kg. Immediate facilitatory effect of LSD on auditory primary responses to paired clicks delivered at 120 msec. intervals between clicks. Paired clicks delivered every five seconds. Facilitation of second response was again the outstanding feature of the excitatory action of LSD (Fig. 4).

The LSD used in these experiments was injected intravenously in graded doses, either buffered or unbuffered. As might be anticipated, the effects to be described were independent of pH on injection. In certain experiments, when a maximum LSD effect was obtained, the subsequent antagonistic action of reserpine was studied.

All potentials were amplified by means of conventional capacity-coupled amplifiers and photographed from the tube face of a dual-beam oscilloscope by means of a Fairchild camera.

For each particular experimental event a single or paired stimulus was employed once every 5-10 seconds to provide a considerable margin of safety for recovery in the primary system under study. It has been shown[13] that the total recovery time in a specific thalamocortical system probably does not exceed five seconds, even under conditions of barbiturate narcosis. In all instances 20-40 single cathode-ray-oscilloscope sweep records were made and only the most constant series used for illustration purposes.

RESULTS

Facilitation of Auditory and Visual Primary Responses with LSD

The facilitatory action of LSD on the evoked auditory primary responses in the unanesthetized cat is shown in Figure 1. To obtain these records, a 10μ-tipped microelectrode was introduced stepwise into the auditory cortex via a micromanipulator. The integrated laminar cortical responses in each new position were recorded after two to three minutes to avoid injury effects. In the control (Fig. 1*A*) the surface-positive response recorded monopolarly (7-9 msec. latency) following the 0.1-msec. click delivered to the contralateral ear shows phase reversal at about 0.6 mm.[14] and reaches maximum negativity in the deeper layers containing the specific afferent terminals. At the completion of the control penetrations, the microelectrode was returned to the surface of the cortex. In Figure 1*B* of records taken five minutes after 40γ/kg. of LSD, I. V., the facilitatory effects of the drug can be seen to consist of a slightly decreased background activity and increased surface positivity, reflecting a marked change in the intracortical negativity. The large sink re-

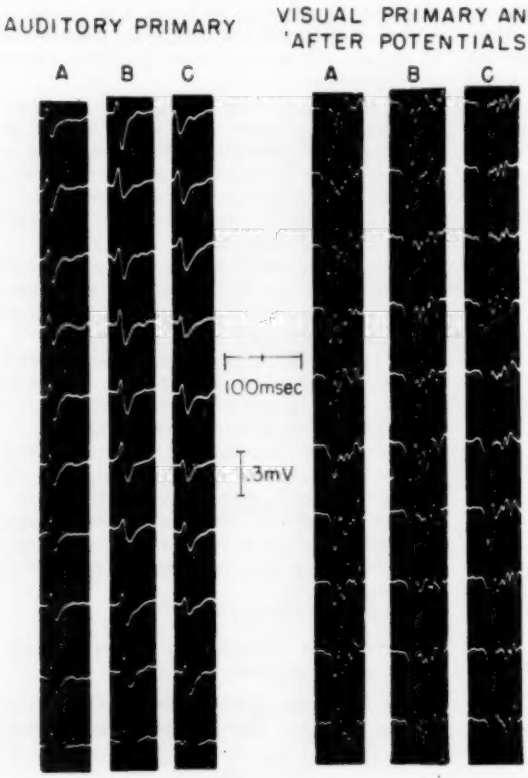


Fig. 6.—Differential action of LSD on evoked auditory and visual primary responses in unanesthetized-paralyzed cat. Explanation in test.

A. Control - 5 hours after termination of ether
B. 25 MIN. after 3μg/K LSD i.v.
C. 25 MIN. after total 30μg/K i.v.

corded at 0.6 mm. in Figure 1*B* represents increased synaptically induced depolarization of cortical neurons by the afferent volley as a result of the LSD.

The general range of spontaneous variability of the auditory primary responses under the experimental conditions described above can be seen in Figure 2 (open circles). The increase may be noted in amplitude recorded after the LSD in the five experiments plotted (solid circles).

Similar facilitatory effects of LSD can be seen on the visual primary response to a brief flash delivered to the atropinized eye of the unanesthetized cat. A typical example of this can be seen in Figure 3 after injection of 5γ/kg., then 20γ/kg., of LSD. Particular attention should be focused on the facilitation of the negative phase of the evoked visual primary response, as well as the W-wave, immediately following the primary.

Another way of demonstrating the facilitatory action of LSD is to study the effects of the drug on the excitability cycle of the specific thalamocortical pathway to paired stimuli.¶ That the auditory pathway mediating the primary response recovers through

¶ Excitability cycles of specific primary projection systems have been studied in the past under a variety of conditions (References 13, 15, and 16). The presence or absence of a supernormal phase in the initial oscillation of excitability is clearly related to the stage of anesthesia and type of anesthetic agent (References 17, 18, and 19).

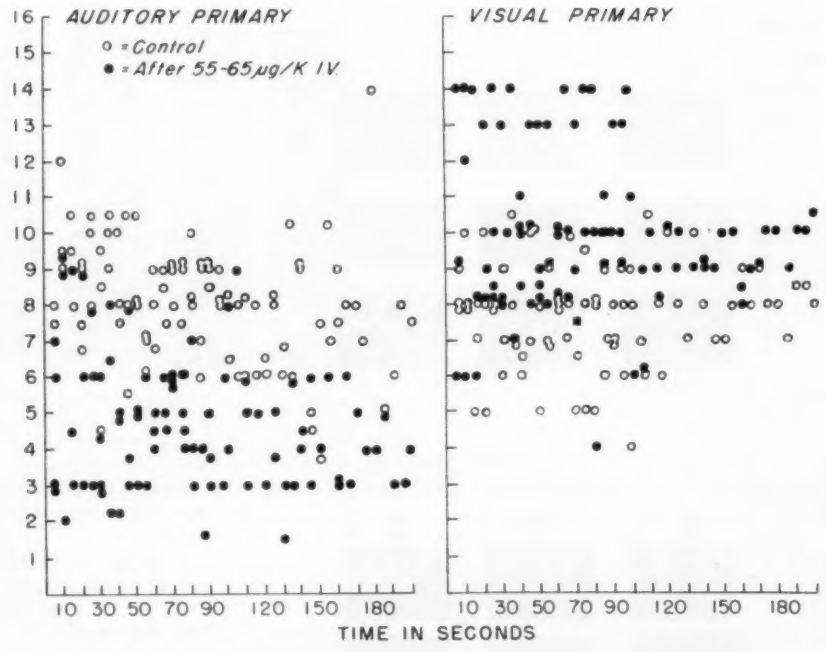


Fig. 7.—Composite graph of three experiments, demonstrating differential inhibition of auditory response by LSD at high concentrations. Auditory and visual stimuli delivered every five seconds for as long as 200 seconds to minimize major excitability fluctuations. Graded doses of LSD, up to 65γ/kg., were given over the course of one hour after the control responses were recorded.

a phase of supernormality [18] can be shown in the control graph of Figure 4, when the second click follows the first after about 65 msec. The sequence of events after graded doses of LSD may be observed to involve a facilitation of the first (conditioning) response, associated with an increase in the amplitude of the testing response, first at the supernormal period (at 2γ/kg.), then to the right (at 4γ/kg.) and the left (at 15γ/kg.) of the general elevation of the recovery curve. The predominant effect of LSD in low doses appears to be one of recruitment of neurons from the subliminal fringe to the discharge zone, thus producing a profound change in the recovery cycle of excitability.

Although maximum facilitation of the evoked primary responses usually required 10-15 minutes to develop, increased excitability could be detected within 2 minutes after intravenous administration of the drug. In Figure 5 it is apparent that the series of double-click responses recorded in the control state are facilitated two minutes after 20γ/kg. of LSD, indicating fairly rapid penetration of the drug across the blood-brain barrier.

It should be mentioned that in moderately deeply barbiturized animals no facilitatory effects could be detected at low concentrations of LSD that produced facilitation of evoked primary responses in the unanesthetized-paralyzed animals.# Inhibi-

The fact that LSD produces an increase in the amplitude of both the positive and the negative components of the primary responses, as well as a shortening of the recovery cycle, indicates a true facilitation of the responses, and not a pseudofacilitation, seen paradoxically when the brain is in a condition of moderate functional depression. In this instance the increased positive component is associated with abolition of the subsequent negative wave and increased recovery time. The paradoxical increase in the positive component has been related to a process of "disocclusion."[20]

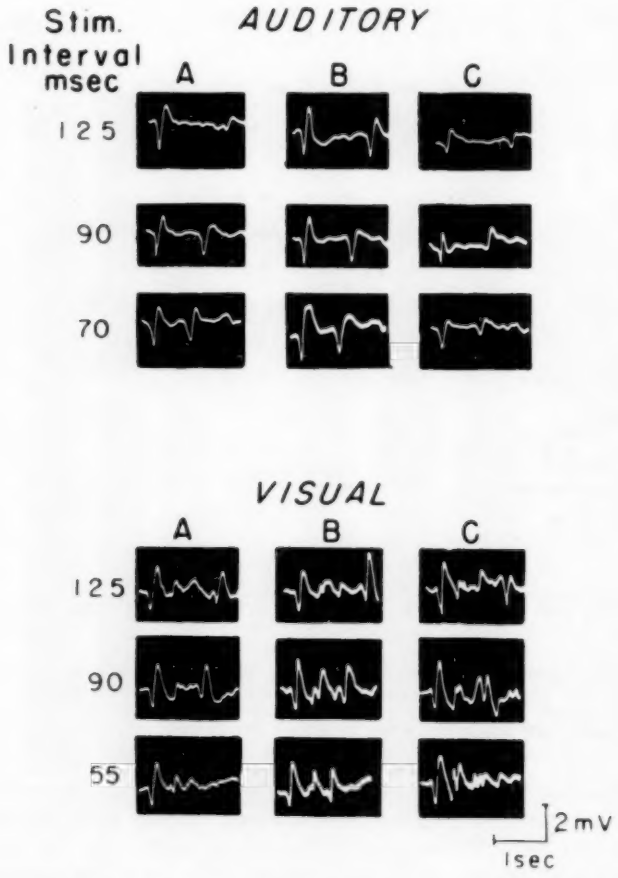


Fig. 8.—Differential action of LSD on auditory and visual recovery cycles. In this experiment paired stimuli were delivered to the ear or eye. The Figure shows examples of the responses at three stimulus intervals. It can be seen that initial facilitation of both systems is followed by differential depression of the auditory system.

A, control; *B*, 15 minutes after LSD, 20γ/kg.; *C*, 30 minutes after total dose of 55γ/kg.

tion of evoked responses regularly occurred in all systems at higher concentrations.

Differential Effects of LSD on Auditory and Visual Primary Responses

An interesting feature of the comparative study of LSD on the audiovisual excitability cycles in the unanesthetized animals has been the observation that following the initial period of facilitation a differential depression of the auditory responses occurred at a higher drug level, while the visual primary responses were still facilitated. This differential action is demonstrated in Figure 6. In this experiment a series of 10 consecutive auditory and visual primary responses were recorded five hours after termination of ether anesthesia. In Figure 6*B* facilitation of both primary responses can be seen after a low dose of LSD. After a total of 30γ/kg. of LSD, depression of the auditory primary responses occurred (Fig. 6*C*), with the development of a prolonged positivity, whereas the visual primary responses remained facilitated. A composite picture of the differential action of LSD at high doses on auditory and visual primary responses is shown in Figure 7, representing the results of three experiments.

Differential effects on the auditory and visual excitability cycles are shown in Figure 8.

Although as much as 60γ/kg. of LSD has been injected in graded fashion, no significant inhibition of the visual primary response to retinal stimulation has been ob-

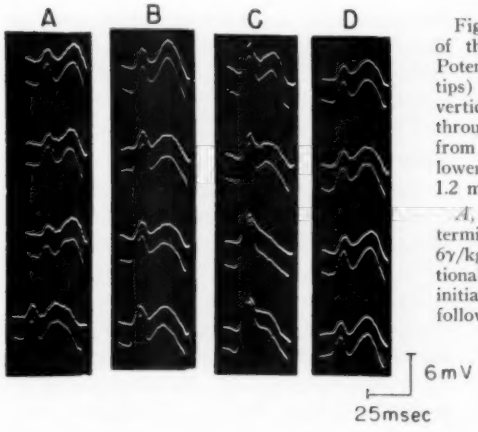


Fig. 9.—Antagonism of LSD-induced facilitation of the auditory primary response by reserpine. Potentials recorded from two microelectrodes (10μ tips) side by side with approximately 1 mm. vertical displacement, and maintained in position throughout the experiment. Upper channel records from superficial electrode, 0.2 mm. in cortex, and lower channel records, from intracortical electrode, 1.2 mm. in auditory cortex.

A, consecutive series control, three hours after termination of ether anesthesia; *B*, 20 minutes after 6γ/kg. of LSD; *C*, 20 minutes after *B* and additional 35γ/kg. Note in particular facilitation of the initial negative response. *D*, 10 minutes after *C*, following 1.5 mg/kg. of reserpine, I.V.

served. A similar invulnerability of the primary response to optic nerve stimulation has been reported after much larger doses of LSD.[21]

Antagonization of LSD Effects by Reserpine

In certain instances, at the conclusion of an experiment in which maximum LSD effects were obtained, the subsequent effect of reserpine on these alterations was studied. A detailed investigation of the action of the latter drug is beyond the scope of the present report. Suffice it to say that reserpine was shown to antagonize the action of LSD whether this action on the auditory primary was facilitatory, at low doses, or inhibitory, at higher doses. Examples of this electrophysiological antagonism are shown in Figs. 9 and 10.

In Figure 9, a series of recordings from a pair of microelectrodes placed at different depths in the auditory cortex is shown in *A* (control) and after 6γ/kg. and 35γ/kg. of LSD, administered over the course of 40 minutes. In Figure 9*D* the effects of 1.5 mg/kg. of reserpine, I. V., can be seen 10 minutes after administration. It is noteworthy that the previously facilitated responses have been reduced to control levels of excitability by the high dose of reserpine.

Antagonism of the depressed auditory primary response can be seen in Figure 10. The control responses used in this Figure are similar to the responses shown in Figure 6*C*. A total of 60γ/kg. of LSD had been injected when the consecutive series of Figure 10*A* were obtained. The facilitation produced by 0.8 mg/kg. of reserpine 15 minutes after injection is apparent in Figure 10*B*.

Although little effect was noted on the spontaneous electrocortical activity of the rabbit after low doses of reserpine, doses

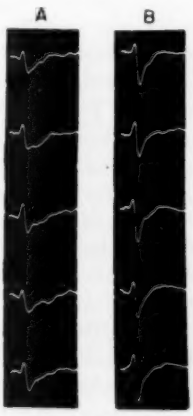


Fig. 10.—Antagonism of the LSD-induced depression of the auditory primary response by reserpine. Records obtained in *A* 6 hours after termination of ether anesthesia and 20 minutes after a total dose of 60γ/kg. of LSD.

similar to those which antagonized the facilitatory action of LSD have been shown to produce "stimulation of the reticular formation," leading to typical arousal patterns in the electrocorticogram.[22] Thus, the action of reserpine on the auditory primary response might be secondary to chemical "arousal" effects. It is common knowledge that the desynchronization of electrocortical activity accompanying stimulation of the ascending brain stem reticular system [23] is associated with reduction in amplitude of primary responses.[24] Attempts to elucidate the action of LSD on the nonspecific reticulocortical activity will be presented in the subsequent report.[26]

COMMENT

The experiments described above have been performed on unanesthetized-paralyzed cats. It is important that this be emphasized to avoid the immediate danger of translating the results obtained in the apparently conscious cat to conscious man under the influence of the psychotogenic agent LSD. It is not possible to determine whether the concentration of LSD which produces the synaptic facilitation in the specific projection systems is associated with hallucinatory phenomena in the cat similar to those seen in man at approximately the same low concentrations. However, it would seem reasonable to assume that an hallucinatory event is associated, at least in part, with an alteration in the recovery cycle of excitability in the primary afferent system. LSD has been shown to produce marked alterations in the recovery cycle of excitability in the primary projection systems in the cat. The demonstration of increased excitability in the visual primary system has already been reported in man under LSD intoxication.[25] That the facilitatory action of LSD on specific projection systems is associated with another mechanism occurring at different synapses will be reported in another communication.[26]

The differential sensitivity to depression of the auditory projection system at high concentrations of LSD which produced continued facilitation of the visual primary responses cannot be adequately interpreted at this time. The existence of discrete biochemical differences in the synaptic mechanisms constituting the two pathways may be a factor for consideration. The subsequent report will treat of this in detail.

The demonstration of LSD antagonization by reserpine shown on the auditory primary response, although of clinical interest, cannot be accepted as evidence supporting a competitive action on a specific enzyme system somewhere in the bioelectric generator mechanism. The fact that a variety of structurally dissimilar agents, i. e., barbiturates, serotonin,[27] and pipradrol,[28] antagonize the various actions of LSD further suggests the possibility of multiple biochemical loci of action of LSD.

SUMMARY

1. The administration of LSD in low concentrations (2γ/kg.-30γ/kg., I. V.) produces facilitation of the evoked auditory and visual primary responses in the unanesthetized-paralyzed cat.

2. This facilitatory action can be demonstrated to involve an alteration in the recovery cycle of excitability.

3. At higher concentrations (40γ/kg.-60γ/kg. of LSD) differential depression of evoked auditory responses occurs, with continued facilitation of the evoked visual primary response.

4. Reserpine antagonizes the action of LSD on the auditory primary response, whether this action be facilitatory or inhibitory.

REFERENCES

1. Stoll, W. A.: Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe, Schweiz. Arch. Neurol. u. Psychiat. **60**:279, 1947.

2. Forrer, G. R., and Goldner, R. D.: Experimental Physiological Studies with Lysergic Acid Diethylamide (LSD-25), A. M. A. Arch. Neurol. & Psychiat. **65**:581 (May) 1951.

3. Rinkel, M.; DeShon, H. J.; Hyde, R. W., and Solomon, H. C.: Experimental Schizophrenia-like Symptoms, Am. J. Psychiat. **108**:572 (Feb.) 1952.

4. Hoch, P. H.; Cattell, J. P., and Pennes, H. H.: Effects of Mescaline and Lysergic Acid (d-LSD-25), Am. J. Psychiat. **108**:579 (Feb.) 1952.

5. Hoagland, H.; Rinkel, M., and Hyde, R.: Adrenocortical Function and Urinary Phosphate Excretion: Comparison in Schizophrenia and in Lysergic Acid Diethylamide-Induced Psychotic Episodes in Normal Persons, A. M. A. Arch. Neurol. & Psychiat. **73**:100 (Jan.) 1955.

6. Osmond, H., and Smythies, J.: Schizophrenia: A New Approach, J. Ment. Sc. **98**:309 (April) 1952.

7. Hoffer, A.; Osmond, H., and Smythies. J.: Schizophrenia: A New Approach: II. Result of a Year's Research, J. Ment. Sc. **100**:29 (Jan.) 1954.

8. Jung, C. G.: Psychology of Dementia Praecox, translated by A. A. Brill, New York, Nervous and Mental Disease Publishing Company, 1936.

9. Bremer, F.: Différence d'action de la narcose éthérique et du sommeil barbiturique sur les réactions sensorielles acoustiques du cortex cérébral: Signification de cette différence en ce qui concerne la mécanisme du sommeil, Compt. rend. Soc. biol. **124**:848, 1937.

10. Forbes, A.; Battista, A. F.; Chatfield, P. O., and Garcia, J. P.: Refractory Phase in Cerebral Mechanisms, Electroencephalog. & Clin. Neurophysiol. **1**:141 (May) 1949.

11. Gastaut, H.: The Brain Stem and Cerebral Electrogenesis in Relation to Consciousness, in Brain Mechanisms and Consciousness, edited by H. Jasper, Oxford, Blackwell Scientific Publications, Ltd., and Springfield, Ill., Charles C Thomas, Publisher, 1954.

12. Li, C.-L.; Jasper, H., and Henderson, L.: The Effect of Arousal Mechanisms on Various Forms of Abnormality in the Electroencephalogram, Electroencephalog. & Clin. Neurophysiol. **4**:513 (Nov.) 1952.

13. Marshall, W.: Excitability Cycle and Interaction in Geniculate-Striate Systems of Cat, J. Neurophysiol. **12**:277 (July) 1949.

14. Cragg, B. G.: The Electrical Responses of Mammalian Cerebral Cortex, J. Physiol. **124**:254 (May) 1954.

15. Bishop, G. H.: Cyclic Changes in Excitability of the Optic Pathway of the Rabbit, Am. J. Physiol. **103**:213 (Jan.) 1933.

16. Jarcho, L. W.: Excitability of Cortical Afferent Systems During Barbiturate Anesthesia, J. Neurophysiol. **12**:447 (Nov.) 1949.

17. Gastaut, H.; Gastaut, Y.; Roger, A.; Corriol, J., and Naquet, R.: Etude électrographique du cycle d'excitabilité cortical, Electroencephalog. & Clin. Neurophysiol. **3**:401 (Nov.) 1951.

18. Rosenzweig, M. R.: Effect of Anesthesia on Refractory Period of Auditory Cortex, Am. J. Physiol. **163**:746P (Dec.) 1950.

19. Clare, M. H., and Bishop, G. H.: The Intracortical Excitability Cycle Following Stimulation of the Optic Pathway of the Cat, Electroencephalog. & Clin. Neurophysiol. **4**:311 (Aug.) 1952.

20. Bremer, F., and Bonnet, V.: An Analysis of the Sensory Responses of the Acoustic Cortex, Electroencephalog. & Clin. Neurophysiol. **1**:447 (Nov.) 1949.

21. Evarts, E. V., and Marshall, W. H.: Effects of LSD on Excitability of the Lateral Geniculate, Tr. Am. Neurol. A., 1955, to be published.

22. Rinaldi, F., and Himwich, H. E.: A Comparison of Effects of Reserpine and Some Barbiturates on the Electrical Activity of Cortical and Subcortical Structures of the Brain of Rabbits, Ann. New York Acad. Sc. **61**:27, 1955.

23. Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455 (Nov.) 1949.

24. Bremer, F.: The Auditory Area of the Brain: An Oscilloscopic Study of Its Activity, in Bremer, F.: Some Problems of Neurophysiology, London. Athlone Press, 1953.

25. Gastaut, H.; Ferrer, S., and Castells, C.: Action de la diéthylamide de l'acide d-lysergique (LSD 25) sur les fonctions psychiques at l'électroencephalogramme, Confinia neurol. **13**:102, 1953.

26. Purpura, D. P.: Electrophysiological Analysis of Psychotogenic Drug Action on Evoked Cortical Potentials: II. General Nature of LSD Action on Central Synapses, A. M. A. Arch. Neurol. & Psychiat., this issue, p. 132.

27. Woolley, D. W., and Shaw, E.: Some Neurophysiological Aspects of Serotonin, Brit. M. J. **2**:122 (July 17) 1954.

28. Fabing, H. D.: New Blocking Agent Against the Development of LSD-25 Psychosis, Science **121**:208 (Feb. 11) 1955.

Electrophysiological Analysis of Psychotogenic Drug Action

II. General Nature of Lysergic Acid Diethylamide (LSD) Action on Central Synapses

DOMINICK P. PURPURA, M.D., New York

With the Technical Assistance of Desmond Callan, A.B.

It has been shown that graded doses of LSD (*d*-lysergic acid diethylamide-25) produce facilitation of evoked auditory and visual primary responses in the unanesthetized-paralyzed cat. At higher concentrations differential depression of the auditory responses was seen to occur while facilitation of the visual responses could still be detected.[14]

The present report extends the observations to include other, nonspecific, afferent pathways and presents evidence relating to the differential action of LSD on various synaptic arrangements.

METHODS

Methods were essentially similar to those reported previously, with the following additions: Recruiting responses were evoked by 5-10/sec. stimulation of the rostral pole of centrum medianum of the thalamus. They were generally recorded maximally from the sensorimotor cortex. Stimuli were delivered through a 0.5 mm. concentric electrode introduced by means of a three-dimensional micromanipulator. In addition to studying the effect of LSD on cortical potentials evoked from a symmetrical point on one hemisphere via the transcallosal pathway after bipolar stimulation of a point on the opposite hemisphere,* the effects of LSD on the pyramidal cells in the optic cortex were investigated. These cortical neurons were activated via the optic radiations and the corticocortical pathway from the lateral half of the suprasylvian gyrus to the optic cortex. In contrast to the responses evoked from the primary optic pathway, which are initiated by cell-body discharges, the latter pathway activates exclusively the apical dendrites of the pyramidal cells.†

To study the action of LSD on the diffuse cortical secondary discharge (Forbes response),‡ the animals were initially anesthetized with larger doses of pentobarbital sodium and maintained in a state of moderately deep narcosis by small additional doses, intravenously. At the completion of experiments dealing with subcortical stimulation of midline thalamic nuclei, the animals' brains were perfused with 10% saline-formalin and sectioned to confirm approximate electrode positions. As in the preceding communication, LSD was injected intravenously in all instances.

RESULTS

Effect of LSD on Nonspecific Afferent Systems

The functional significance of the diffuse thalamocortical system mediating the recruiting response has been described and studied in detail elsewhere.§ The reciprocal functional relationship between the activity in the upper and that in the lower brain stem reticular system [13] presumably underlies the difficulty of obtaining low-threshold recruiting responses in alert animals. This was confirmed in the present investigation. Not

Received for publication Aug. 2, 1955.

Presented in part at the 80th Annual Meeting of the American Neurological Association, Chicago, June 13, 1955.

Special Research Fellow, National Institute of Neurological Diseases and Blindness, U. S. Public Health Service.

From the Laboratory of the Department of Neurological Surgery, Columbia University College of Physicians and Surgeons.

* References 1 and 2.

† References 3 and 4.

‡ References 5 to 7.

§ References 8 to 12.

only was the excitable region from which one could obtain recruiting responses greatly reduced, but there also occurred a general elevation in threshold for excitation in the relatively unanesthetized-paralyzed animals. Despite this, however, it can be seen in Figure 1 (control records obtained nine hours after initial barbiturization) that 5γ/kg. of LSD decreased the excitability of the recruiting response system at a time when concomitant testing of the auditory and visual primary responses were facilitated. Additional LSD in this experiment produced further depression of the recruiting response strated in another experiment (Fig. 2). Inhibition of these responses evoked with supramaximal stimulation of the centrum medianum occurred in this instance after 45γ/kg. of LSD. Similarly, by adjusting the thalamic stimulus to threshold values for obtaining the responses, almost complete inhibition was detected (Fig. 3) in another experiment. An interesting feature of the inhibitory action of LSD on the responses was the persistence of the surface-negative component of 15- to 20-msec. duration and the inability of the responses to recruit effectively. The behavior of these responses under

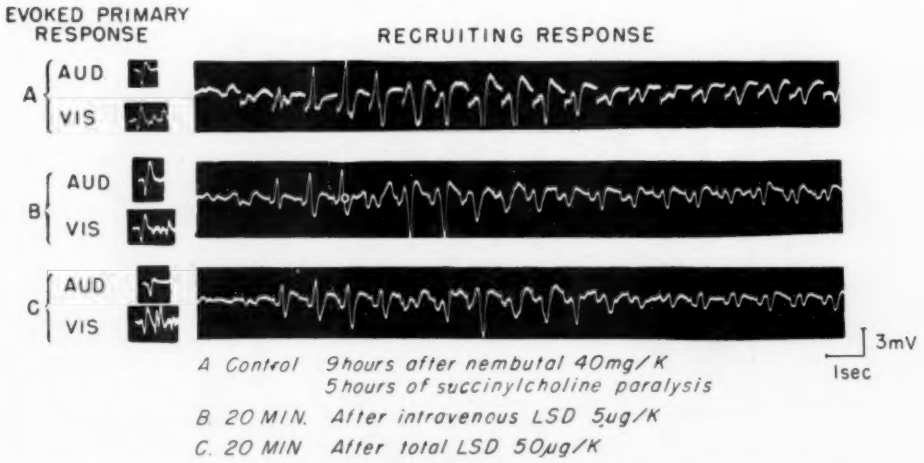


Fig. 1.—Differential effects of LSD on specific and nonspecific thalamocortical systems (auditory, visual, and recruiting responses). Recruiting responses were recorded from sensorimotor cortex following 10/sec. stimulation of centrum medianum of thalamus. In particular, it should be noted that after 5γ/kg. of LSD enhancement of the auditory and visual primary responses occurred, with slight depression of the recruiting responses. After a total of 50γ/kg. of LSD, depression of the auditory primary responses can be seen, along with continued depression of the recruiting responses and facilitation of the primary visual potentials. Facilitation of visual "after-potentials" can be seen in *C*, as previously reported.[14]

and differential depression of the auditory primary response [14] with continued enhancement of the visual primary response.

By shortening the time from the initial injection of pentobarbital to the beginning of the control runs, thereby increasing the excitability of the recruiting mechanism, it was observed that smaller concentrations of LSD produced more pronounced inhibition of the recruiting responses evoked from the sensorimotor cortex. This is graphically demonstrated in another experiment (Fig. 2). Inhibition of these responses evoked with supramaximal stimulation of the centrum medianum occurred in this instance after 45γ/kg. of LSD. Similarly, by adjusting the thalamic stimulus to threshold values for obtaining the responses, almost complete inhibition was detected (Fig. 3) in another experiment. An interesting feature of the inhibitory action of LSD on the responses was the persistence of the surface-negative component of 15- to 20-msec. duration and the inability of the responses to recruit effectively. The behavior of these responses under the conditions noted above is consistent with the proposed dendritic nature of this activity,‖ a factor of the utmost importance, which will be treated below in detail. It should be mentioned that the inhibitory effect of LSD on the recruiting responses was reversible, recruitment returning to near-

‖ Bishop, G. H., and Clare, M. H.: Facilitation and Recruitment in Dendrites, presented at the Ninth Annual Meeting, American Electroencephalographic Society, Chicago, June 11, 1955.

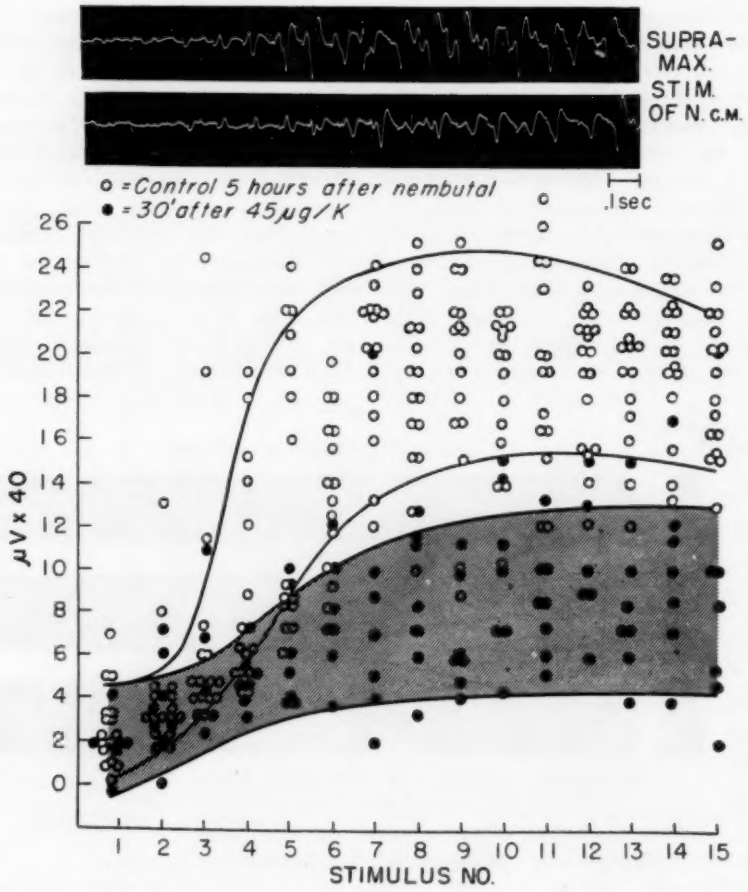


Fig. 2.—Inhibition of "recruiting response" by LSD.

Abscissa: First 15 consecutive stimuli of the 10/sec. stimulus to centrum medianum.

Ordinate: Amplitude of the recruiting responses recorded from sensorimotor cortex.

Open circles: Scatter of 16 control series of recruiting responses recorded over a 30-minute period, demonstrating general range of variability of the responses.

Solid circles: Scatter of seven runs obtained after maximum LSD effect.

Inset records: Upper: Sample recruiting response from posterior sigmoid gyrus. Lower: Inhibited responses after LSD. Note persistence of the 20-msec. negative deflections and minimal recruitment by the seventh shock, as contrasted with the maximal recruitment by the fifth shock of the stimulus train in the control records.

normal within one hour after maximum LSD action.

Effects of LSD on the Forbes "Secondary Discharge"

The high degree of susceptibility to inhibition of the nonspecific thalamocortical recruiting mechanism may be considered a reflection of the differential inhibitory action of LSD on the slowly conducting multisynaptic elements comprising the core of the brain stem. This is further demonstrated by the differential effect of LSD on the Forbes "secondary discharge." Previous studies have shown that this long-latency, generalized response, optimally obtainable under conditions of moderate barbiturate narcosis,¶ is generated by collateral affer-

¶ References 5 and 6.

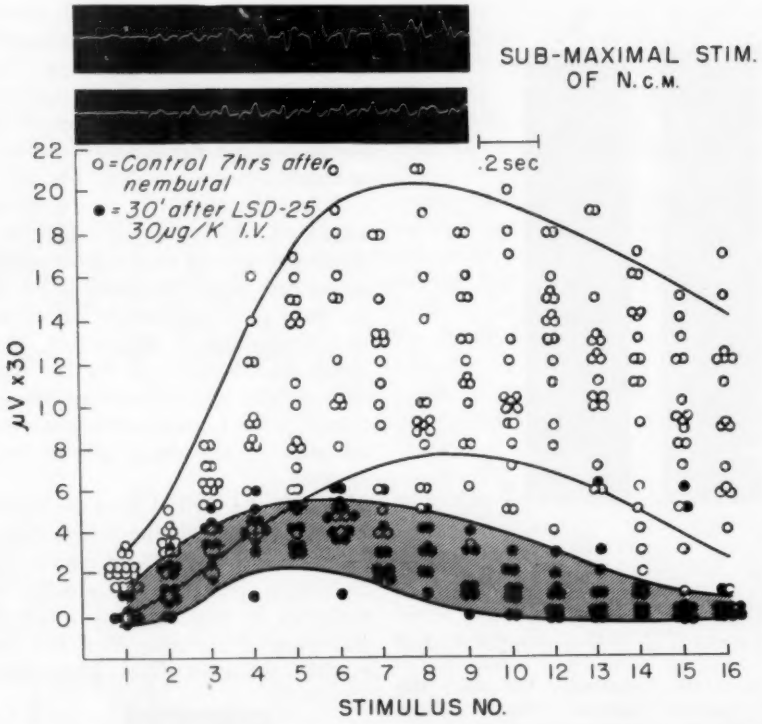


Fig. 3.—Essentially similar to Figure 2. In this experiment submaximal stimulation of centrum medianum evoked recruiting responses (upper inset records), which attained maximal voltage by the fourth shock of the train, then exhibited alternation. In the lower record, complete inhibition of recruitment can be seen, with persistence of the 20-msec. negative deflection, assignable to dendritic activity (see text for further details).

Open circles: Scatter of 16 control series over 30-minute period.

Closed circles: Inhibition responses after LSD.

ents leaving the primary pathway and utilizing an extralemniscal pathway to the cortex.[15] All the features of this response may be reproduced by single-shock stimulation of the medial brain stem reticular system, and the functional significance of this has been discussed elsewhere.[7] The fact that the Forbes response may also be obtained in the unanesthetized animal and man [16] is inconsistent with the hypothesis that it is an artifact of anesthesia.

The effect of LSD on this reticulocortical discharge may now be considered. The secondary discharges to five consecutive shocks to the proximal end of the right sciatic nerve can be seen in Figure 4*A*. These responses were recorded monopolarly from the contralateral anterior marginal gyrus, a somesthetic association area in the cat.[17] In Figure 4*B* the complete blockade of the secondary discharge can be seen within 15 minutes after injection of 20γ/kg. of LSD. Despite the presence of moderate barbiturate narcosis employed in the experiments on the "secondary discharge," the differential inhibitory action of LSD on this long-latency discharge to sensory stimulation could be detected. This is clearly shown in Figure 5. On the upper channel the auditory primary response has been recorded, and on the lower channel the secondary discharge to sciatic stimulation has been recorded from the somesthetic association area. It should be noted that the "secondary discharge" to

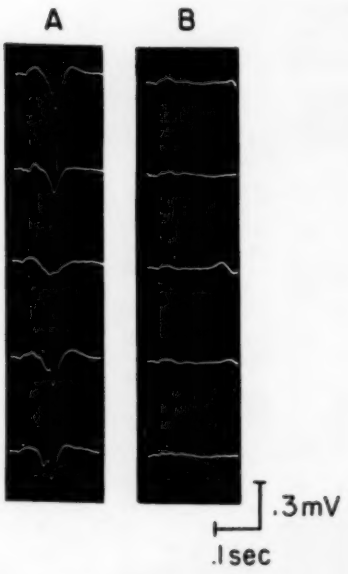


Fig. 4.—*A*, five consecutive "secondary discharges" (controls) following sciatic stimulation recorded from the contralateral anterior marginal gyrus. Moderately deep barbiturate narcosis. Stimulus interval, five seconds.

B, complete inhibition of the responses 15 minutes after 20γ/kg. of LSD.

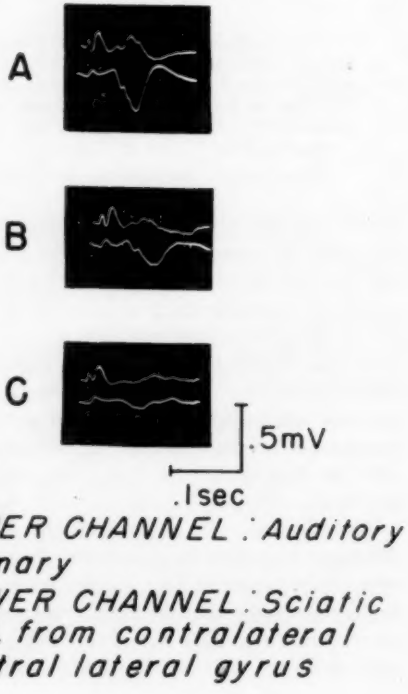
Fig. 5.—Differential inhibition of "secondary discharge" by LSD. Upper channel records: Auditory primary response to click stimulation of right ear recorded from left anterior ectosylvian gyrus. Note also slow negative generalized "secondary discharge" recorded from same site after simultaneous sciatic stimulation. Lower channel records: "Secondary discharge" following sciatic stimulation recorded from the anterior lateral gyrus.

A, control; *B*, after 10γ/kg. of LSD; *C*, three minutes after *B*. Almost complete inhibition of the "secondary discharge" can be seen without significant alteration in the auditory primary response. After LSD no change occurred in the depth of anesthesia.

sciatic stimulation recorded from the auditory cortex (upper channel) is characteristically surface-negative.[7] It can be seen that five minutes after 10γ/kg. of LSD marked inhibition of the "secondary discharge" has occurred without significant alteration of the auditory primary response (Fig. 5*C*).

Since barbiturates have repeatedly been shown to augment the Forbes "secondary discharge" and the recruiting-response mechanism, the direct inhibitory action of LSD on these two responses is further evidence of LSD-barbiturate antagonism. Of greater significance, however, is the fact that LSD differentially inhibits these responses in the relatively low concentrations employed without affecting the specific afferent projection systems.

The results derived from the experiments reported above and elsewhere [14] demonstrate a dual action of LSD on central synapses, facilitation occurring in specific afferent pathways at concentrations which produce inhibition of reticulocortical and thalamocortical pathways. This information sug-



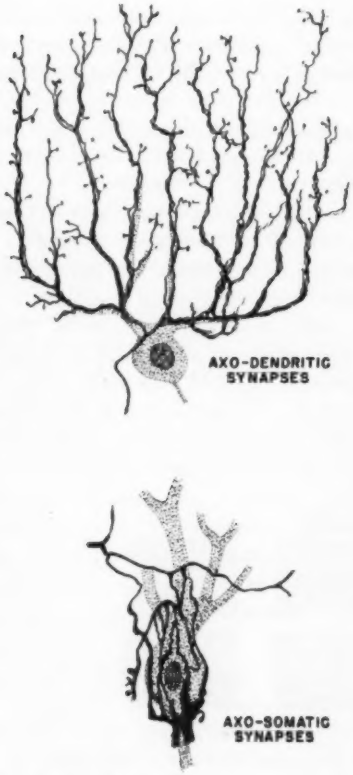


Fig. 6.—Axodendritic and axosomatic synapses on a Purkinje cell in the cerebellum of man (after Ramón y Cajal).

Above, synapses on dendrites of Purkinje cells formed by the climbing fibers, and, below, synapses on cell body of the same cell from basket cells in the molecular layer.

gested that the dual action of LSD was dependent on the synaptic interrelations between the neurons mediating the various evoked responses.

Anatomicophysiological Nature of Central Synapses

The extensive investigations of Cajal # and other, more recent investigations [20] have demonstrated that the interrelations between neurons may be classified as either axosomatic or axodendritic in nature. In the former type of interrelation the synaptic knobs of the telodendron or collaterals of one neuron make contact with the other on the surface of the cell body (pericorpuscular, Chang [20]). The axodendritic (paradendritic, Chang [20]) synapse is described as a neuronal interrelation in which the presynaptic terminals of one neuron make contact with the other on the gemmules of the dendrites. The classical example illustrating the anatomical configuration of the two kinds of synaptic arrangement can be found in the Purkinje cells of the cerebellum, which possess purely axodendritic synapses from the climbing fibers and purely axosomatic synapses from the basket cells in the molecular layer (Fig. 6).

The anatomical distribution of the two types of synapses have been summarized by Chang [20] as follows:

> It seems to be a rule that the central neurons which are subjected to wide spread facilitatory and inhibitory influences such as the large cells in the reticular formation have long and many branched dendritic processes. On the other hand, the neurons in the relay nuclei of the sensory system in which a faithful and prompt transmission of afferent messages is required are mainly surrounded by the peri-corpuscular (axo-somatic) synaptic knobs. The neurons in the Clark nuclei, nuclei gracilis et cuneati, the dorsal and ventral acoustic nuclei, the medial and lateral geniculate bodies have typical peri-corpuscular synapsis.

To this account should be added the anatomical, as well as physiological, evidence

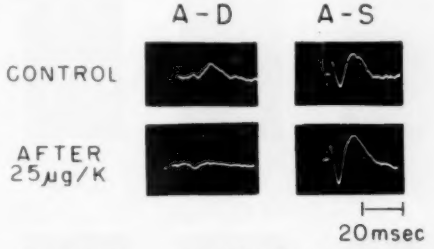


Fig. 7.—Differential inhibition of axodendritic (*A-D*) synapse and facilitation of axosomatic (*A-S*) synapse after LSD.

Control upper left: Dendritic activity evoked in the optic cortex following stimulation of suprasylvian axons.

Control upper right: Striate response to optic radiation stimulation recorded from same cortical site.

Lower left: Inhibition of negative dendritic activity after LSD without effect on the initial positive deflection signaling approach of presynaptic volley.

Lower right: Facilitated striate response after LSD.

References 18 and 19.

indicating that the intercortical * corticocortical association [4] and nonspecific thalamocortical fibers [23] synapse in relation to the dendrites of cortical neurons (axodendritic synapses). Although the question as to whether the nonspecific cortical afferents described by Lorente de Nó originate in the thalamic nuclei giving rise to the recruiting response remains unanswered, physiological data support the axodendritic nature of the synapses mediating the recruiting response.†

* References 21 and 22.

† A more detailed account of corticocortical circuits involving dendritic activity, as well as an analysis of the physiological properties of cortical dendrites, appears in References 3, 4 and 24. The importance of the preliminary data evaluating the functional significance of cortical dendrites cannot be too strongly emphasized (Jasper and Ajmone-Marsan.[11] Bishop, G. H., and Clare, M. H.: Facilitation and Recruitment in Dendrites, presented at the Ninth Annual Meeting of the American Electroencephalographic Society, Chicago, June 11, 1955).

The admittedly brief account presented above has provided a basis for interpreting the dual effect of LSD on central synapses.

The Hypothesis Tested: Differential Action of LSD on Axosomatic and Axodendritic Synapses

It has been shown that stimulation of axons whose cell bodies are located in the lateral half of the suprasylvian gyrus evokes a surface-negative cortical response of 15-msec. duration in the optic cortex. This is attributed to activation of the apical dendrites of vertically oriented pyramidal cells. The physiological properties of the dendrites activated in this manner have been studied in detail elsewhere.[3] In contrast to this axodendritic pathway, activation of pyramidal cell bodies is initiated by a 1- to 2-msec. spike when stimuli are delivered to the optic radiations. The latter type of activity is therefore generated via an axosomatic pathway.

In Figure 7 the effects of LSD on these two pathways can be seen. The upper left oscillogram in this Figure shows the dendritic response following activation of the axodendritic pathway described above, and that on the right, the striate response recorded from the same locus after axosomatic activation of the same neurons via the radiations. Below these control records can be seen the effect of 25γ/kg. of LSD. This consisted of inhibition of the axodendritic activity and slight facilitation of the axosomatic activity.

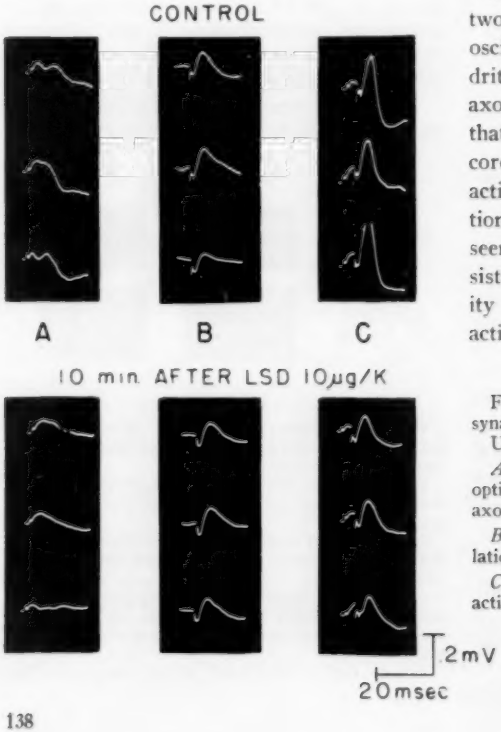


Fig. 8.—Selective inhibition of axodendritic synapse by LSD.

Upper control records:

A, three consecutive responses recorded from the optic cortex following subliminal stimulation of axodendritic pathway from suprasylvian gyrus.

B, (control), striate responses to radiation stimulation.

C, facilitated striate responses when dendritic activation precedes radiation response by 5 msec.

Lower records: After 10γ/kg. of LSD selective inhibition of the catelectrotonic-facilitatory effect of dendritic activation on the striate response can be seen.

The differential action of LSD on the two types of cortical synapse may be tested in another way. It has been shown that a suitably timed volley delivered via the axodendritic pathway will facilitate the striate response to radiation stimulation.[8] This was confirmed in the following experiment: In Figure 8 it can be seen that stimulation of the axodendritic pathway evoked a small surface-negative response in the optic cortex and that stimulation of the radiations with a weak shock generated a striate response whose amplitude was enhanced when the dendritic activity preceded the radiation stimulation by 5 msec. Below these records it is apparent that 10γ/kg. of LSD completely inhibited the catelectrotonic-facilitatory action of the preceding dendritic activation on the striate response.

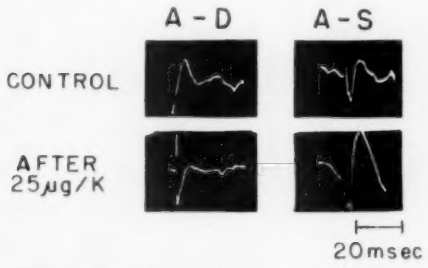


Fig. 9.—Control records:

Upper left: Transcallosal response recorded in optic cortex to stimulation of symmetrical point on contralateral cortex, representing axodendritic (*A-D*) activity.

Upper right: Striate response to radiation stimulation.

Lower left: Inhibition of transcallosal response after 25γ/kg. of LSD.

Lower right: Marked facilitation of striate response.

The selective inhibition of the axodendritic activity was demonstrated in still another manner by employing the transcallosal pathway from the optic cortex on one side to the symmetrical point on the opposite hemisphere. Simultaneous testing of the striate response to radiation stimulation was also carried out. In this instance 25γ/kg. of LSD inhibited the transcallosal response, confirming previous results,[25] but markedly facilitated the striate response (Fig. 9).

COMMENT

The predicted inhibitory action of LSD on the axodendritic synapse and the facilitatory effect on the axosomatic synapse of pyramidal neurons in the optic cortex has provided a basis for interpreting the general nature of LSD action on the evoked potentials of the cat's brain.

Although the anatomical data are incomplete, the electrophysiological data support the axodendritic nature of the synapses on the neural elements giving rise to the recruiting responses following activation of the nonspecific thalamocortical system.‡ Similarly, activation of transcallosal [21] and other corticocortical association pathways [4] appear to involve only excitation of dendrites.

It has been shown that the responses involving chiefly activation of cortical dendrites are markedly inhibited or blocked by the psychotogenic drug LSD. With this specific inhibition of the axodendritic activity a concomitant facilitation of axosomatic activity may be detected in the specific afferent projection pathways.[14] The type of neuronal interrelation in the specific projection system is of the axon-cell-body type, although, as pointed out by Glees,[26] both types of synapse occur in the lateral geniculate body of the cat, with a predominance of axodendritic synapses. In addition to certain operational differences, this may explain in part the finding of Evarts and Marshall [27] that postsynaptic responses recorded from the lateral geniculate body of the cat following single-shock stimulation of the optic nerve were depressed by high doses of LSD, whereas the striate response seemed relatively unaffected.

It is beyond the scope of this paper to discuss the physiological properties of dendrites in detail. For the purposes of the present discussion, it suffices to restate what has previously been said,[4] that the duration of response of the dendrites is much longer than that of the axon or cell

‡ Reference 11. Bishop, G. H., and Clare, M. H.: Facilitation and Recruitment in Dendrites, presented at the Ninth Annual Meeting, American Electroencephalographic Society, Chicago, June 11, 1955.

body; dendrites have no true, absolutely refractory period; they may support local activity at a stimulated region without propagation of impulses to their cell bodies, and then affect their cell bodies by altering the excitability of the latter to impulses reaching them directly. The inhibition of LSD of dendritic activity synaptically induced via association and nonspecific mesodiencephalic pathways terminating on cortical dendrites may in part explain the disorganization of behavioral activity described in man under the influence of this psychotogenic agent. This would support the hypothesis that much of the highly integrative processes involving complex neuronal interrelations is carried on at the neuropil-like axodendritic level. Associated with this inhibition of axodendritic activity is another property of LSD, i. e., a facilitatory action on specific projection pathways mediating incoming sensory signals.§

The hypothesis presented above may perhaps explain some of the experimental results obtained by other investigators. Bradley and Elkes [38] noted abolition of barbiturate spindle activity in the EEG of the cat after relatively large doses of LSD. This flattening was not accompanied by an alteration in the depth of anesthesia. A similar occurrence was reported in the rabbit.[39] This particular electrographic pattern (8-12/sec. spindle) has long been thought to represent the activity of the nonspecific thalamocortical mechanism which on repetitive stimulation gives rise to the recruiting response. Bishop and Clare || have proposed that the recruiting phenomenon represents summated dendritic potentials to inadequate repetitive stimuli.¶ The recruiting response is inhibited by LSD. The results reported by Marrazzi on the effect of LSD on the transcallosal response, confirmed in the present study, become explicable in terms of the anatomical nature of the synapse mediating this response, i. e., axodendritic.[21]

The demonstration of a dual action of LSD on different synaptic patches located on functionally different components of the neuron confirms the existence of dissimilar properties of the bioelectric generator of neuronal potentials. This is further shown by the observation that the dendrites of the pyramidal cells in the optic cortex remain electrically excitable when they are no longer neurally (synaptically) excitable after LSD. This is evident by the increased negative phase of the striate response to radiation stimulation, indicating antidromic propagation along the apical dendrites [41] at a time when synaptic activation of the same dendrites is blocked. It is apparent, therefore, that mammalian

§ Reports are available which discuss the role of certain degradation products of epinephrine in the etiology of schizophrenia (References 28 to 30). These naturally occurring degradation products are said to be structurally related to LSD via an indole nucleus. It is of considerable interest, therefore, to note that epinephrine, like LSD, exerts a dual action on different functional systems. Although Marrazzi [21] has reported only central synaptic inhibition with epinephrine, other workers have consistently reported a dual action of epinephrine on spinal reflex activity (References 31 to 34). As summarized by Skoglund,[35] the intra-arterial injection of 50γ of epinephrine produces facilitation of monosynaptic extensor and depression of multisynaptic flexor reflexes. Facilitation of leg movement following electrical stimulation of the motor cortex with low doses of epinephrine and inhibition with high doses have also been reported.[36] Adrenergic links have been reported to constitute the chains of reticular neurons affecting caudal and cephalic activity.[37]

|| Bishop, G. H., and Clare, M. H.: Facilitatory and Recruitment in Dendrites, presented at Ninth Annual Meeting of American Electroencephalographic Society, Chicago, June 11, 1955.

¶ Bishop and Clare have also proposed that the prolonged potential changes occurring in dendrites under repetitive stimulation may account for all slowly oscillating potentials, such as give rise to the EEG. Tasaki and associates [24] proposed a similar hypothesis, and Jung [40] has also emphasized the importance of these D. C. potential changes. If this hypothesis is confirmed by future investigations, it is reasonable to suggest that the flattening of the EEG produced by LSD may represent an alteration in the excitability cycle of cortical dendrites which prevents summation of synaptic responses. The correlation of the electrocortical flattening after LSD with the electrographic alteration accompanying "arousal" responses to high-frequency stimulation of the brain stem does not seem to be justified at this time. As mentioned previously,[14] the relationship of EEG pattern to distinct states of awareness is not clearly defined.

neurons possess distinct neurally and electrically excitable membrane components, similar in many ways to the dual excitable systems in the electroplaque of the electric eel [42] (see "Addendum").

If the action of the psychotogenic drug LSD on central neurons is dependent on differences in the bioelectric properties of postsynaptic patches (receptors?) on dendrites and cell bodies, it would appear that no single biochemical mechanism of action of LSD is probable. As pointed out previously, this not only may explain the numerous biochemical alterations reported to be produced by LSD # but may also serve to explain why so many structurally dissimilar agents are capable of effectively antagonizing the various behavioral effects of LSD. In view of this, it is appropriate to recall the admonition of Gerard [36]:

> Different agents, different receptors, different impulses, different geometry, and different membrane properties and environment will insure that successful overriding generalizations remain few and that the particulars of each case will long depend on experimental demonstration rather than on logical inference.

Whether or not the dual excitatory and inhibitory action of LSD demonstrated on the evoked cortical potentials of the cat's brain adequately explains the psychic disorganization and hallucinations described in man under LSD intoxication certainly cannot be evaluated at this time.

SUMMARY

The effect of LSD on evoked recruiting responses following stimulation of midline thalamic structures is compared with the previously demonstrated effect on specific primary responses. Differential inhibition of the recruiting responses occurs at concentrations which cause facilitation in the specific systems.

Examination of the primary and Forbes' "secondary discharge" discloses differential inhibition of the latter response with relatively small doses of LSD.

The excitatory action of LSD on specific afferent systems and the inhibitory action on nonspecific and corticocortical systems is explained on the basis of the anatomical nature of the two different types of synapse in the various systems. It is proposed that LSD inhibits axodendritic synapses and facilitates axosomatic synapses.

This dual action is believed to result from differences in the bioelectric properties of dendrites and cell bodies.

ADDENDUM

Since completion of these studies, it has been found that the dendritic elements responsible for the surface-negative wave of 15- to 20-msec. duration are electrically inexcitable at the peak of synaptic inhibition produced by tubocurarine (2-3 mg/kg. I.V.).[47] Since this response can only be elicited by synaptic action, it is inferred that the synaptically excitable membrane components of apical dendrites are also differentially affected by LSD. This suggests the existence of more than one synaptic transmitter (or receptor) whose liberation (or action) is dependent on the source of afferent stimulation. Further evidence for the existence of a wide variety of physiological trigger mechanisms has recently been summarized.[48]

Dr. J. Lawrence Pool gave unfailing support and interest in these investigations, and Dr. Harry Grundfest, invaluable constructive criticism and suggestions.

REFERENCES

1. Curtis, H. J.: Intercortical Connections of Corpus Callosum as Indicated by Evoked Potentials, J. Neurophysiol. **5**:407 (Sept.) 1940.

2. Curtis, H. J.: An Analysis of Cortical Potentials Mediated by the Corpus Callosum, J. Neurophysiol. **5**:414 (Sept.) 1940.

3. Clare, M. H., and Bishop, G. H.: Properties of Dendrites: Apical Dendrites of the Cat Cortex, Electroencephalog. & Clin. Neurophysiol. **7**:85 (Feb.) 1955.

4. Clare, M. H., and Bishop, G. H.: Dendritic Circuits: The Properties of Cortical Paths Involving Dendrites, Am. J. Psychiat. **111**:818 (May) 1955.

References 28 and 43 to 46.

5. Forbes, A., and Morison, B. R.: Cortical Response to Sensory Stimulation Under Deep Barbiturate Narcosis, J. Neurophysiol. **2**:112 (March) 1939.

6. Forbes, A.; Battista, A. F.; Chatfield, P. O., and Garcia, J. P.: Refractory Phase in Cerebral Mechanisms, Electroencephalog. & Clin. Neurophysiol. **1**:141 (May) 1949.

7. Purpura, D. P.: Further Analysis of Evoked "Secondary Discharge": A Study in Reticulo-Cortical Relations, J. Neurophysiol. **18**:246 (May) 1955.

8. Morison, R. S., and Dempsey, E. W.: A Study of Thalmo-Cortical Relations, Am. J. Physiol. **135**:281 (Jan.) 1942.

9. Dempsey, E. W., and Morison, R. S.: The Production of Rhythmically Recurrent Cortical Potentials After Localized Thalamic Stimulation, Am. J. Physiol. **135**:293 (Jan.) 1942.

10. Jasper, H. H.: Diffuse Projection Systems: The Integrative Action of the Thalamic Reticular System, Electroencephalog. & Clin. Neurophysiol. **1**:405 (Nov.) 1949.

11. Jasper, H. H., and Ajmone-Marsan, C.: Thalamo-Cortical Integrating Mechanisms, A. Res. Pub. Nerv. & Ment. Dis., Proc. **30**:493, 1952.

12. Brain Mechanisms and Consciousness: A Symposium, Oxford, England, Blackwell Scientific Publications, Ltd., and Springfield, Ill., Charles C Thomas, Publisher, 1954.

13. Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**: 455 (Nov.) 1949.

14. Purpura, D. P.: Electrophysiological Analysis of Psychotogenic Drug Action: I. Effect of LSD on Specific Afferent Systems in the Cat, A. M. A. Arch. Neurol & Psychiat., this issue, p. 122.

15. Morison, R. S.; Dempsey, E. W., and Morison, B. R.: On the Propagation of Certain Cortical Potentials, Am. J. Physiol. **131**:744 (Jan.) 1941.

16. Brazier, M. A. B.: Studies on Electrical Activity of the Brain in Relation to Anesthetics, in Neuropharmacology, Transactions of the First Conference, Josiah Macy, Jr. Foundation, New York, 1955.

17. Amassian, V. E.: Studies on Organization of a Somesthetic Association Area, Including a Single Unit Analysis, J. Neurophysiol. **17**:39 (Jan.) 1954.

18. Ramón y Cajal, S.: Textura del sistema nervioso del hombre y de los vertebrados, Madrid, N. Moya, 1899-1904.

19. Ramón y Cajal, S.: Les Preuves objectives de l'unite anatomique des cellules nerveuses, Trav. lab. recherches biol. Univ. Madrid **26**:1, 1934.

20. Chang, H. T.: Cortical Neurons with Particular Reference to the Apical Dendrites, Cold Spring Harbor Symposia on Quantitative Biology, 1952, Vol. 17, p. 189.

21. Chang, H. T.: Cortical Response to Activity of Callosal Neurons, J. Neurophysiol. **16**:117 (March) 1953.

22. Bremer, F.: Interaction, dans l'aire auditive du chat, des influx transmis par le corps calleux et des influx sensoriels spécifiques: Interprétation physiologique des données oscillographiques, Rev. neurol. **87**:162, 1952.

23. Lorente de Nó, R.: Cerebral Cortex: Architecture, Intracortical Connections, Motor Projections, in Physiology of the Nervous System, edited by J. F. Fulton, New York, Oxford University Press, 1953.

24. Tasaki, I.; Polley, E. H., and Orrego, F.: Action Potentials from Individual Elements in Cat Geniculate and Striate Cortex, J. Neurophysiol. **17**:454 (Sept.) 1954.

25. Marrazzi, A. S., and Hart, E. R.: Evoked Cortical Responses Under the Influence of Hallucinogens and Related Drugs, Electroencephalog. & Clin. Neurophysiol. **7**:146 (Feb.) 1955.

26. Glees, P.: Termination of Optic Fibers in Lateral Geniculate Body of the Cat, J. Anat. **75**: 434 (July) 1941.

27. Evarts, E. V., and Marshall, W. H.: Effects of LSD on Excitability of the Lateral Geniculate, Tr. Am. Neurol. A., 1955, to be published.

28. Hoagland, H.; Rinkel, M., and Hyde, R.: Adrenocortical Function and Urinary Phosphate Excretion: Comparison in Schizophrenia and in Lysergic Acid Diethylamide-Induced Psychotic Episodes in Normal Persons, A. M. A. Arch. Neurol. & Psychiat. **73**:100 (Jan.) 1955.

29. Osmond, H., and Smythies, J.: Schizophrenia: A New Approach, J. Ment. Sc. **98**:309 (April) 1952.

30. Hoffer, A.; Osmond. H., and Smythies, J.: Schizophrenia: A New Approach: II. Result of a Year's Research, J. Ment. Sc. **100**:29 (Jan.) 1954.

31. Marrazzi, A. S.: Cholinergic Excitation and Adrenergic Inhibition Common to Peripheral and Central Synapses, in The Biology of Mental Health and Disease, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952, p. 376.

32. Bülbring, E., and Burn, J. H.: An Action of Adrenaline on Transmission in Sympathetic Ganglia, Which May Play a Part in Shock, J. Physiol. **101**:289 (Nov.) 1942.

33. Bernhard, C. G.; Skoglund, C. R., and Therman, P. O.: Studies of the Potential Level in the Ventral Root Under Varying Conditions, Acta physiol. scandinav. (Supp. 47 [art. 8]) **14**:1, 1947.

34. Bülbring, E.; Burn, J. H., and Skoglund, C. R.: The Action of Acetylcholine and Adrenaline on Flexor and Extensor Movements Evoked by Stimulation of the Descending Motor Tracts, J. Physiol. **107**:289 (June) 1948.

35. Skoglund, C. R.: Spinal Cord and Sympathetic Ganglia, Factors That Modify Transmission Through the Spinal Cord, Cold Spring Harbor Symposia on Quantitative Biology, 1952, Vol. 17, p. 233.

36. Gerard, R. W.: Summary, Symposium on Neurohumoral Transmission, Pharmacol. Rev. **6**: 123 (March) 1954.

37. Dell, P.; Bonvallet, M., and Hugelin, A.: Tonus sympathique adrénaline et contrôle reticulaire de la motoricité spinale, Electroencephalog. & Clin. Neurophysiol. **6**:599 (Nov.) 1954.

38. Bradley, P. B., and Elkes, J.: Effect of Amphetamine and LSD-25 on Electrical Activity of the Brain of the Conscious Cat, J. Physiol. **120**: 13P (April) 1953.

39. Delay, J.; Lhermitte, F.; Verdeaux, G., and Verdeaux, J.: Modifications de l'électrocorticogramme du lapin par la diéthylamide de l'acide d-lysergique (LSD-25), Rev. neurol. **88**:81, 1952.

40. Jung, R.: Symposium on the Physiological Basis of the EEG: Symposia of III International Congress of Electroencephalography and Clinical Neurophysiology (Aug., 1953), Electroencephalog. & Clin. Neurophysiol., Supp. 4, 1954.

41. Bishop, G. H., and Clare, M. H.: Site of Origin of Electric Potentials in Striate Cortex, J. Neurophysiol. **15**:201 (May) 1952.

42. Altamirano, M.; Coates, C. W., and Grundfest, H.: Mechanisms of Direct and Neural Excitability in Electroplaques of Electric Eel, J. Gen. Physiol. **38**:319 (Jan.) 1955.

43. Mayer-Gross, W.; McAdam, W., and Walker, J.: Lysergsäure-Diäthylamid und Kohlenhydratstoffwechsel, Nervenarzt **23**:30, 1952.

44. Poloni, A., and Maffezzoni, G.: Le Variazion dell'attività cholinergica del tessuto cerebrale per effetto della bulbocapnina, della mescalina e della dietilamide dell'acido lisergico, Sistema nerv. **4**: 578, 1952.

45. Lewis, J. L., and McIlwain, H.: The Action of Some Ergot Derivatives, Mescaline and Dibenamine on the Metabolism of Separated Mammalian Cerebral Tissues, Biochem. J. **57**:680, 1954.

46. Thompson, R. H. S.; Tickner, A., and Webster, G. R.: Cholinesterase Inhibition by LSD, Biochem. J. **58**:19, 1954.

47. Purpura, D. P., and Gundfest, H.: Fed. Proc., to be published.

48. Grundfest, H.: Excitation Triggers in Post-Junctional Cells, J. Cell. & Comp. Physiol. **46**: 368, 1955.

News and Comment

SOCIETY NEWS

New Jersey Neuropsychiatric Association.—The following officers elected for the year 1956:

Past president.....J. Lawrence Evans Jr., M.D., Englewood
President.....Evelyn Parker Ivey, M.D., Morristown
President-elect.....Ira S. Ross, M.D., South Orange
Secretary.....Robert S. Garber, M.D., Princeton
Treasurer.....William Furst, M.D., East Orange
Trustees.....

David W. McCreight, M.D., Marlboro
Leon Reznikoff, M.D., Weehawken
John L. Kelly, M.D., New Brunswick
Floyd Fortuin, M.D., Paterson
Robert Mearin, M.D., Montclair
William Boutelle, M.D., Somerville

Hereditary (Familial) Spastic Paraplegia

Further Clinical and Pathologic Observations

GABRIEL A. SCHWARZ, M.D.
and
CHAN-NAO LIU, Ph.D., Philadelphia

A review of the clinical, and especially the neuropathologic, data on the heredofamilial form of spastic paraparesis or paraplegia was presented in 1952.[1] In this report there were included a pedigree and clinical studies of some of the members of a family designated as Family Ze. Since that time, one of us (G. A. S.) has had the opportunity of examining a younger member of this family who has recently developed the disease. Clinical studies of another family have been acquired. Finally, we obtained the central nervous system of one of the afflicted members of the Ze family for pathologic study. We felt that the presentation of all this newly acquired material would significantly extend the earlier report.

CLINICAL AND PATHOLOGIC REPORTS IN THE LITERATURE

The reports of Rhein,[2] Paskind and Stone,[3] Price,[4] Bell and Carmichael,[5] and Schwarz [1] gathered the numerous clinical and pathologic studies of this disease contained in the literature from Seeligmüller's original study,[6] in 1876, to about 1950. Altogether, at least 181 families in which a spastic weakness or spastic paralysis of the lower extremities had occurred in a variable number of their members were found to be chronicled in the world's medical writings. Since then, the following further observations have been reported:

Appel [7] described the clinical findings in three of seven brothers whose father had developed a painful, progressive difficulty in walking when he was 50 years old. One afflicted brother began at the age of 20 years to have stiffness of both his lower extremities. When examined at the age of 43, this man showed a marked spasticity, but practically no weakness, of the muscles of his lower extremities. He had generally hyperactive tendon and periosteal reflexes, active abdominal and cremasteric reflexes, ankle clonus, and Hoffmann, Rossolimo, and Mendel-Bechterew signs, but no sign of Babinski. His two afflicted brothers actually had not had any complaints, but the 54-year-old brother was found to have hyperactive reflexes in the left upper extremity and in both lower extremities with suggestive Rossolimo signs, while the 39-year-old brother displayed somewhat accentuated reflex activity throughout with bilateral Hoffmann and Rossolimo signs.

André-Thomas, Ajuriaguerra, and Vargues [8] detailed the clinical findings in a 34-year-old man, who first complained of heaviness in his lower extremities at the age of 33. This man had a moderately spastic gait with remarkably good power in his lower extremities. The hypertonus of the muscles of his lower extremities was felt by the authors to be especially significant. They found hyperactive tendon and periosteal reflexes throughout with bilateral ankle and patellar clonus and signs of Babinski, Rossolimo, and Mendel-Bechterew. There were also impaired diadokokinesia in the upper extremities, a slow and monotonous speech, and thoracic kyphosis. The authors were able to trace the disease through three generations

Received for publication Aug. 8, 1955.

This study was supported in part by the Kirby-McCarthy Fund.

From the Departments of Neurology and Anatomy, University of Pennsylvania School of Medicine.

of his family. They found 10 afflicted persons, 6 of whom were male, and noted that the age of onset was usually between the ages of 20 and 30 years. The gait disorder was rapidly progressive in this family, so that within three or four years they were unable to walk. More than half the afflicted members had a progressive speech difficulty. Three members of the third generation were mentally retarded. Yet, despite their disease, they lived a long time. Transmission was felt to be dominant in this family.

Garland and Astley [9] reported a family in which the disease could be traced through three generations. Nine members were affected. They examined seven of these. Their patients began to have trouble in walking at the ages of 11 or 12 years. All of them had had very slow progression of the spastic weakness of their lower limbs. As an example of the clinical picture presented by the disease in this family, the authors described their findings in a 31-year-old mechanic. His gait was spastic and slightly "scissors" in type, but with no ataxia. No changes were noted in his upper extremities. His abdominal reflexes were present, and the tendon reflexes in his lower extremities were brisk, with bilateral ankle clonus and Babinski's sign. He had a well-marked pes cavus on both sides and diffuse wasting of the muscles below his knees. There was good power in his lower limbs, though definite weakness of dorsiflexion of his feet and of extension of his toes was noted. There was spasticity of both lower extremities. This pattern, in varying degrees of severity, was noted in all seven of their cases. The authors felt that the amyotrophy was not due to disuse, that the pes cavus was not produced by the amyotrophy, and that transmission here was as a Mendelian dominant, with the same gene producing the pes cavus, the amyotrophy, and the spastic paraplegia.

Curcio [10] described the clinical findings in a man of 29 and his two sisters, all of whom had a progressive weakness of their lower extremities. The man began to have trouble in walking at the age of 13, and at the same time began to have difficulty in talking. He had progressive weakness of his lower limbs, but also of his upper limbs. He showed hypertonia of his four extremities (more marked in the lower); quadriparesis; generalized hyperreflexia with bilateral ankle and patellar clonus; bilateral Babinski's sign; impaired abdominal reflexes; some disturbances in touch, vibration sense, and position sense in the lower extremities; impaired nonequilibratory coordination; dysarthria, and emotional lability. His older sister developed a disturbance in walking at the age of 17 years. She had a progressive disorder, for by the age of 38 she could no longer walk or stand. She had impaired power in all her extremities, but especially the lower, with hyperreflexia and a bilateral ankle clonus and Babinski's sign. She also had a slight tremor of her upper extremities and bilateral pes cavus. Their younger sister began to have pain and weakness in her left lower extremity when she was 12 years old. By the time she was 24 years old, besides her spastic gait, she had a thoracic lordoscoliosis, bilateral pes cavus, bilateral hypertonia and hyperreflexia with the sign of Babinski, quadriparesis, and cerebellar signs in the upper extremities. There had never been a disease like this in their family before, and their two siblings were healthy.

Alajouanine and Nick [11] detailed the clinical findings in two brothers. The older boy had never really been normal. He had had nystagmus from birth and had never been able to stand or walk alone. By the age of 14 years, he was found to display many neurologic deficits—bedfastness, inability to stand, tremor of his head when sitting, hypertonus-in-extension of his lower extremities, hypotonia of his upper extremities and neck and trunk, marked incoordination (cerebellar) in his upper extremities, generally impaired muscle power, hyperreflexia in his lower limbs with bilateral clonus and Babinski's sign, hyporeflexia in his upper extremities, disturbances in micturition, dysarthria, dysphagia, nystagmus, facial weakness, impairment of voluntary upward gaze,

and mental retardation. A pneumoencephalogram revealed cerebral atrophy and moderate ventricular dilatation. The younger brother was generally flaccid after birth, and at the age of a year had some convulsive seizures. When he was examined at the age of 11½ years, his condition was much like that of his brother, with minor differences, such as, for instance, an athetoid quality in the disturbed movements of his upper extremities and bilateral abducens weakness. There were no other afflicted members of their family. The authors felt that these neurologic disturbances were familial, and not acquired.

Appel and van Bogaert [12] described a second family in which four persons (possibly five, for the grandmother was said to have had a bizarre gait) were afflicted in three generations. The authors gave clinical details of three siblings (a female and two males) from the third generation. The female ("Elza") never walked or talked or was mentally normal. She was practically quadriplegic, for her upper extremities were flexed and spastic and poorly mobile, while her lower limbs presented paraplegia-in-extension. She had generalized hyperreflexia with loss of abdominal reflexes and the sign of Babinski bilaterally. A paraplegia-in-flexion with contracture finally developed, and she died of pulmonary tuberculosis at the age of 22. Her next younger brother ("Roger") began to develop walking movements but never did stand or walk alone. He never talked. He had a spastic quadriparesis, with his upper limbs held in flexion and his lower limbs in extension. There were hyperactive tendon reflexes throughout, absence of abdominal and cremasteric reflexes, bilateral ankle and patellar clonus, bilateral sign of Babinski, and a cervical kyphosis. He died of tuberculosis at the age of 22. Their younger brother ("Jean") developed normally until the age of 3 years, when he began to have a stumbling gait. He was able to say a few words slowly before his speech became involved. The disturbances were progressive, so that by the age of 18 years he was bedfast with a spastic quadriplegia, mute, mentally retarded, dysphagic, and incontinent for urine. He died at 19 years of age, probably of tuberculosis.

Histologic studies of the nervous systems of "Elza" and "Roger" were reported by Appel and van Bogaert.[12] In the girl they found the following changes: degeneration of the crossed and direct pyramidal tracts from the lumbar region of the spinal cord up through the medulla into the pons; gliosis of these degenerated tracts; mild degeneration and gliosis of Goll's columns, traceable into the medulla; small pyramids; multiple areas of gliosis in various widely separated portions of the neuraxis—olivary capsules, dentate nuclei, substantia nigra, etc.—small areas of old necrosis in the cerebellum, one optic nerve, and basal ganglia, felt not to be quantitatively significant; marked reduction of Betz cells in Brodmann's Areas 4, 6, and 8 of the cerebral cortex; vacuolar-granular changes in the small and medium-sized pyramidal cells of Laminae III and V; heterotopic pyramidal cells in Lamina I, and a diffuse cellular gliosis in all layers, especially Lamina III, and similar cortical gliosis in the parietal area. In the boy they found the following changes: degeneration of the crossed pyramidal tracts from the bottom of the spinal cord to the pons; degeneration of Goll's columns throughout the spinal cord; gliosis of the posterior part of the lateral columns, the posterior columns, the pyramids, and various portions of the brain stem, cerebellum, and basal ganglia; in the cerebral cortex, a reduced number of Betz cells and of the small and medium-sized pyramidal cells of Laminae III and V, with proliferation of the macroglia of Areas 4, 6, and 8 of Brodmann.

These same authors [13] reported on a third family in which three boys in the third generation had spastic paraplegia and various other members showed mental retardation. The maternal grandparents of the boys had had no neurologic disease, and neither had their five children (two boys, three girls). Two of these girls married two mentally dull brothers, and their descendants pre-

sented the abnormalities. One sister had five children: a girl who had a harelip and died of convulsions at 2 months of age; two boys with spastic paraplegia; a boy who was said to have been similarly afflicted and died at 2½ years, and a girl who died of convulsions at the age of 4 weeks. The other sister had five children: two girls who were oligophrenic (one with epilepsy also), the others with no neurologic disorder. The authors detailed the histories and findings in the two paraplegic brothers. The older boy ("Jean") did not walk until the age of 27 months, and then only on the tips of his toes. He never did speak. At 3½ years of age it was first noted that his upper extremities were also involved. He had a progressive spastic paraparesis-in-extension. His upper extremities were held in flexion. He was a "tranquil idiot." As time went by, he became more disabled, had trouble in swallowing, and finally developed spastic quadriplegia, with absence of abdominal reflexes and the sign of Babinski bilaterally. He died at the age of 10 years of pulmonary tuberculosis. At the age of 6 months his younger brother ("Raymond") was noted to hold his lower limbs close together with the feet turned down and in, while the upper limbs were held close to the body and semiflexed. Within two years he had spastic quadriplegia with hyperactive tendon reflexes, intact abdominal reflexes, and a bilateral sign of Babinski. He had intermittent convergent strabismus and right facial palsy. He developed abnormal involuntary movements of his head, jaw, and tongue. Before he died, at the age of 9 years, he had marked spastic quadriplegia-in-flexion — indeed, he was totally rigid.

In studying the nervous system of one of these brothers ("Jean"), Appel and van Bogaert [13] noted the following picture: degeneration and fibrillary gliosis of the pyramidal tracts in the spinal cord; in the cervical cord, an oval dilation of the ependymal canal, surrounded by a dense gliosis, extending into the gray matter and posterior columns; similar changes in the lower areas of the spinal cord; pyramids smaller than usual with moderate gliosis; Betz cells apparently normal in number, and no other cellular changes in the motor or premotor cortex. The authors felt that an element of dysraphism or of syringomyelia might be present at times in family spastic paraplegia.

Landau and Gitt [14] recorded an extensive family tree of 283 members, of whom 21 had "related" neurologic disturbances. The authors examined 8 afflicted members, obtained medical records on 5 more, examined many asymptomatic members, and found 14 members who were felt to have early forms of this neurologic disease. They found clinical evidence of unrelated neurologic disease in 10 other members of the family. On the basis of the clinical findings, the authors divided their patients into four groups: (1) pyramidal system disease predominating, becoming clinically evident in adult life; (2) cerebellar symptoms prominently mixed with the pyramidal symptoms; (3) amyotrophies of adult life clinically identical with amyotrophic lateral sclerosis, and (4) rapidly progressive involvement, beginning early in adolescence and resulting in fatal bulbar destruction. The most consistent finding was the pyramidal system involvement, but the lower motor neuron, the cerebellum, and the extrapyramidal system were always involved, in variable degrees and combinations, in the affected members of this family. The authors felt that the responsible genetic defect was a single dominant gene with modifiers and partial sex-linkage in the main gene or in the modifiers.

Michaux, Teysseyre, and Fandre [15] recorded a family in which one member was afflicted in each of three generations. The grandmother began to have trouble in walking at the age of 12 years. One of her sons began to have his gait difficulties at the age of 12 years. Of his seven children, a daughter began to drag her left foot at the age of 12 years. When examined at the age of 14 years, this girl showed dorsolumbar kyphoscoliosis and spastic paraparesis. It was noted how spastic her gait was and how

hypertonic her lower limb muscles were, yet what good power she still had in the muscles of her lower limbs. She had hyperreflexia in her lower extremities with intact abdominal reflexes and a bilateral sign of Babinski. She was mentally retarded. The authors could demonstrate no involvement of the upper extremities, but the chronaxie values suggested to them that there was preclinical involvement at this level.

Heuyer, Lebovici, and Seignot, at a meeting of the Pediatric Society of Paris,[16] described the neurologic findings in two sisters. There was no history of neurologic disease in the patient's family. The two children (aged 4 years and 2 years 11 months at the time) had developed their symptoms at the age of 15 months. The elder child had spastic quadriplegia, a bilateral Babinski sign, athetotic movements of the left upper extremity, tonic attacks, and progressive dementia. The younger child had spastic paraplegia-in-extension and bilateral Babinski and Rossolimo signs but was not mentally affected. On clinical grounds, and because of the early age of onset, relatively rapid progression, and mental regression, the authors felt that the children were not afflicted with "familial spastic paraplegia of Strümpell-Lorrain," but with Schilder's disease.

Aceto [17] recorded the clinical findings of a boy of 2 years. His three brothers and a sister had spastic tetraplegia also—thus, of 14 children, 5 were afflicted. The author's patient could not sit, stand, walk, or talk. He had quadriparesis, with his upper limbs in flexion and his lower limbs in extension. Muscle power was not markedly disturbed; mobility was limited, and spasticity was more marked in the lower limbs. He had generally lively tendon reflexes, hypoactive abdominal reflexes, and the sign of Babinski bilaterally. He had some atrophy of the optic nerve heads and was mentally dull.

Appel and van Bogaert [18] described another family in which the parents were healthy, but of their 10 children, 2 boys and a girl developed spastic paraplegia and one other girl was a feebleminded deaf-mute. The afflicted girl began to have difficulty in walking at the age of 42. Her four living children were healthy. She had kyphosis in the cervical-thoracic area, a spastic gait, remarkably good power in her lower extremities, hyperactive tendon reflexes throughout, preserved abdominal reflexes, bilateral patellar and ankle clonus, and the sign of Babinski bilaterally. One of her afflicted brothers began to have painful cramps in his legs at the age of 50; then tightness of his thighs, and fatigue of his lower extremities by the age of 59. Thereafter, he had progressive weakness of his lower limbs. When examined at the age of 69, this man had spastic paraparesis, generally hyperactive tendon reflexes, preserved abdominal and cremasteric reflexes, bilateral Babinski and Oppenheim signs, and slight impairment of position sense in both lower limbs.

They studied the nervous system of the afflicted woman and found no changes in her motor or premotor cortex. There was degeneration and gliosis of the pyramidal tracts in the spinal cord, especially the crossed tracts, and involving the direct tracts hardly at all. The pyramidal degeneration ceased in the upper cervical region and was not traceable in the brain stem. Throughout the spinal cord, they noted degeneration of the anterior horn cells, especially the posteromedian groups and somewhat the anteromedian groups. Only in the cervical portion of the spinal cord did they find a slight demyelination of the tracts of Goll and Burdach. A sieve-like state of the putamen, pigmentary changes in the substantia nigra, and rarefaction of the olivary nuclei were felt to be unrelated findings, due to the age of the patient. From this case and their previous pathologic observations, they concluded that the more rapid and severer forms of this disease damaged the cortex, while the more slowly progressive forms produced only spinal cord changes.

Van Bogaert [19] recorded yet another family in whose first generation a man began to have slowly progressive spastic paraparesis at the age of 18. Optic atrophy began at

the age of 20, and by the time he was 30 years of age he was blind. At the age of 40 he had spastic quadriplegia with slight amyotrophy of his hands. Of this man's six children, only one son had a progressive spastic paraplegia, which began at the age of 15. He also had a progressive optic atrophy, which led to blindness in four years. In the third generation of this family there were 14 children; 3 of these (2 girls and a boy) developed spastic paraplegia. The boy was the son of the only afflicted sibling of the second generation, and he showed spastic quadriparesis, adiadokokinesia, slight atrophy of the thenar and hypothenar eminences, a bilateral Babinski sign, impaired vibration sense and position sense in the left hand, sphincter difficulties, and temporal pallor of his optic nerve heads. He became progressively more spastic, had further diminution of his vision, and lost vibration sense below his clavicles. A girl whose mother was one of the unafflicted siblings of the second generation began to have trouble at the age of 14½ years in the form of abnormal fatigability and stiffness of her lower extremities. She had a progressive spastic paraparesis, thoracic kyphoscoliosis, and some urinary urgency. By the age of 38 she was quadriplegic with sphincter difficulties. Another girl ("Henriette"), whose mother was also one of the asymptomatic siblings of the second generation, began to have trouble in walking at the age of 16. Urinary difficulties were apparent by the age of 24. At this time there was also slight atrophy of the muscles of her calves, thighs, thenar eminences, and the backs of her hands. She had a spastic quadriparesis. Her tendon reflexes were lively throughout, with patellar and ankle clonus, absence of abdominal reflexes, and a bilateral sign of Babinski. She had no ocular abnormalities. She developed a severe urinary tract infection and bronchopneumonia, and died at the age of 24½.

This patient's (i. e., "Henriette's") nervous system showed an intact cerebral cortex, including the motor and premotor areas. Nothing of significance was noted in the other portions of the cerebrum or in the cerebellum. There was slight gliosis of the region of the pyramidal tracts in the cerebral peduncles and pallor with gliosis of the pyramidal portions of the pons and the medulla. A similar fiber loss with slight gliosis was noted near the nuclei of Goll and Burdach in the medulla. In the cervical portion of the spinal cord, the pyramidal tracts were definitely paler than usual, and fibrillary gliosis was apparent in the posterior columns, especially in Goll's tracts. In the lower thoracic, lumbar, and sacral portions, thinning of the crossed and uncrossed pyramidal tracts was apparent. The posterior column gliosis was not seen below the second thoracic level. The anterior horn cells, spinal roots, and striated muscles were unaltered histologically. The pathologic changes were felt to represent a degenerative process with glial organization.

Analyzing their four families * from the genetic viewpoint, van Bogaert [20] decided that three showed a dominant inheritance and only one [13] the recessive form. He felt that in none was the condition sex-linked.

Nayrac and Warot [21] described the clinical findings in two sisters, whose three siblings and parents were healthy. One of the sisters began to have trouble in walking at the age of 19 years. She was bedfast in three years. She had spastic paraplegia-in-extension with hyperactive reflexes and bilateral ankle clonus and sign of Babinski. Her sister was mentally retarded and began to have trouble in using her lower extremities when she was 23 years old. She showed severe oligophrenia, marked myopia, and spastic paraparesis. It was noted that the muscle power in her lower extremities was not greatly impaired and that the spasticity was less when she was lying down.

Dick and Stevenson [22] recorded four generations of a family in which there were seven afflicted members. In the first generation, a male member had had a slight tremor of his right arm and the toes of his feet ever since his youth. In his midmaturity he began to have trouble in walking. Of his six chil-

* References 12, 13, 18, 19.

dren, five were afflicted (three girls, two boys). Two of the girls were severely crippled and never walked. The third girl began to have pain in her legs at the age of 9 years and soon thereafter developed a progressive spastic paraplegia-in-extension. One of the boys of the second generation began to have progressive weakness of his left lower extremity at the age of 10 years, weakness of his right lower extremity at the age of 20, and abnormal involuntary movements of his head and all his extremities at the age of 30. The spastic weakness of his lower extremities gradually progressed, until he was bedridden at the age of 65, while the abnormal movements persisted. The other boy began to have stiffness of his lower limbs at the age of 10 years. This slowly progressive paraparesis was accentuated by the development of extrapyramidal rigidity and abnormal involuntary movements of his extremities in his late 40's. The latter had a daughter (two sons were normal) who dragged her right foot at the age of 5 years and then gradually developed a spastic paraparesis. At 18 years of age writhing movements began in her toes.

Refsum and Skillicorn [23] described the neurologic findings in two siblings (a man of 22 and a girl of 17). They had had a brother who had had an identical neurologic disorder before he died, at the age of 29. Their illness began between the ages of 3 and 5 years. In each it began with spastic weakness of the lower limbs. Progression was slow, but inevitably the upper extremities were involved, and finally the lower cranial motor nerves. Progressive muscular wasting with fasciculations occurred during their adolescence. They all developed marked skeletal deformities. At the time of the examination, they presented a neurologic picture "indistinguishable from amyotrophic lateral sclerosis." The early age of onset and the prolonged course made the authors feel that this was not an example of the family form of amyotrophic lateral sclerosis.

Thus, 16 families included under the title of "hereditary (or familial) spastic paraplegia" have been recorded in the medical literature since 1950. A study of these clinical reports indicates that the one common element in all of these cases was the presence of a spastic hyperreflexic paraparesis or paraplegia (but often a quadriplegia!). Yet many other neurologic deficits coexisted in most of the clinical reports, such as speech difficulty,† mental retardation,‡ pes cavus,§ sensory disturbances,‖ incoordination and tremors,¶ abnormal involuntary movements,# amyotrophy,* optic atrophy,† and so forth. Indeed, if one peruses the details of the histories and clinical records of these families, it is difficult to see any certain relationship of the various families which would allow them to be grouped together under one title. Some authors feel that "hereditary spastic paraplegia" is an all-embracing group, as did Rhein.[2] Our objection to such a loose grouping has been voiced previously.[1]

Of special interest are the five neuropathologic reports ‡ which have been published since 1950. While they all appear under the same clinical heading, neither the histories nor the pathologic findings seem to us to be uniform enough to justify such handling. For instance, the authors' first three cases § were really speechless, feebleminded quadriplegics from birth and showed numerous changes in various portions of the neuraxis. Their fourth case [18] clinically suggested a "pure" spastic paraparesis, but the authors found changes in certain of the anterior horn cells. Their fifth case [19] had muscle wasting, as well as a spastic paraparesis; yet the anterior horn cells were found to be intact. Of course, in each case they found degeneration and gliosis of the pyramidal tracts of the spinal cord. It would seem, therefore, that at least part of the

† References 8, 10-13, 17.
‡ References 8, 11-13, 15, 16, 21.
§ References 9 and 10.
‖ References 10, 18, and 19.
¶ References 10, 11, 14, and 22.
# References 13, 14, 16, and 22.
* References 14, 19, and 23.
† References 17 and 19.
‡ References 12, 13, 18, and 19.
§ References 12 and 13.

marked variation in the recent (and past) pathologic findings in hereditary (familial) spastic paraplegia is due to the fact that the clinical boundaries are much too broad. Perhaps a more rigid clinical designation of cases to be included in this group in the future might obviate some of the present inconsistencies in the pathologic data.

REPORT OF FAMILY ED.

The information on this family was obtained from our patient, Edward Ed. He stated that his mother and father had never had any trouble in walking (Fig. 1). His brother, 16 months younger, is said to have had progressive weakness of his lower extremities since birth. A sister of his mother had six children. One of these cousins, a woman, began to have weakness of her lower extremities at the age of 42. Her walking disorder had also slowly progressed.

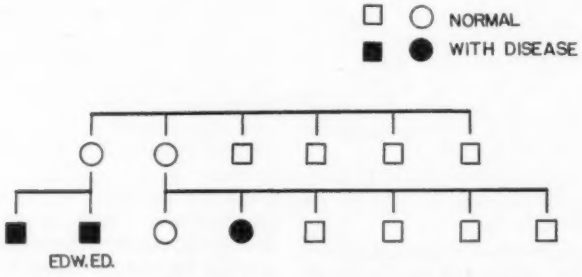


Fig. 1.—Pedigree of Family Ed. The three afflicted members of this family were married but had no children.

Our patient, Edward Ed., was seen in the diagnostic clinic of the University of Pennsylvania Hospital in October, 1954, at the request of Dr. H. Gordon Guyler. The patient was born in 1905.

He first noted difficulty in walking down an incline at the age of 41. Thereafter, he had recognized a gradual progression in the impairment of his ability to use his lower extremities, but he seemed to be annoyed more by the stiffness of his gait than by any weakness. He stated that his feet had been "high-arched" ever since he could remember.

The neurologic examination showed the cranial nerves to be intact. The patient's gait was obviously spastic in type; yet he walked quite freely. There was no swaying in the Romberg position. There was no dysmetria, dyssynergia, or dysdiadokokinesia. His sensory system was intact for touch, pain, vibration sense, position sense, and graphesthesia. There was little demonstrable weakness of the muscles of his lower extremities. There was increased tone of the muscles of his lower extremities when he was standing; yet when he was supine and relaxed, there was no evidence of increased muscle tone in his lower extremities. No wasting of muscles and no fasciculations were noted. The tendon and periosteal reflexes were equally active in the upper extremities. Hoffmann's sign was not present. The abdominal reflexes were equally active on the two sides. The tendon reflexes of his lower extremities were hyperactive, with ankle clonus and Rossolimo and Babinski signs bilaterally. The formation of both feet suggested pes cavus.

Laboratory studies showed a hemoglobin of 102% (15.91 gm. per 100 cc.) and 5600 leucocytes per cubic millimeter of blood. Of these, 64% were polymorphonuclear cells and 36% were lymphocytes. Urinalysis showed a faint trace of sugar. Postprandial blood sugar was 118 mg. per 100 cc. The Queckenstedt test revealed no block of the spinal subarachnoid space. Cerebrospinal fluid studies revealed no cells, protein of 44 mg. per 100 cc., a nonreactive Kolmer test, and a negative colloidal mastic test. The blood serum Kolmer and Kline tests were nonreactive. Skull, chest, and spine roentgenograms revealed nothing of significance.

FURTHER DATA ON THE ZE. FAMILY
REPORT OF NEW CASE IN SIXTH GENERATION
(Fig. 2)

C. Ze. was born in 1920. His father was G. Ze., who is afflicted with this disease. He has a brother (born in 1927) and a sister (born in 1923) who have no trouble in walking. They are both married and have healthy young children.

The patient was first seen in neurologic consultation, at the request of Dr. George W. Heintzelman, on May 7, 1953. He was then 33 years of age. He is married and has a male child (born Feb. 12, 1952), who is said to present no neurologic symptoms. C. Ze. dated the onset of his own difficulties to about the age of 30. He stated that he first noted that his gait was unsteady. He would drag his feet, for they felt stiff and heavy. He could

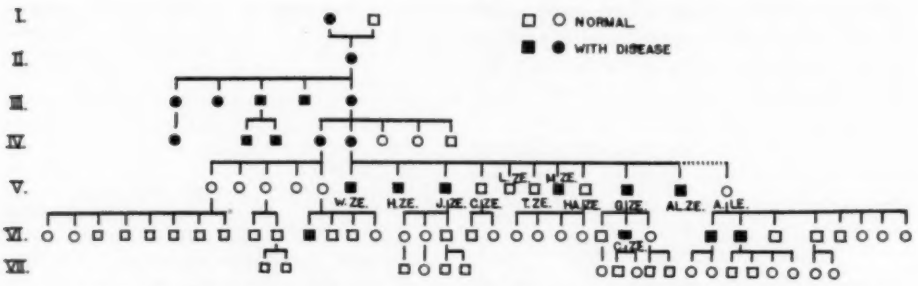


Fig. 2.—Revised pedigree of Family Ze. In the fifth generation, *A. Ze.* was born first, before the 10 boys, but was of different paternity. *H. Ze.* had "epilepsy" and died at the age of 29. *L. Ze.* died of typhoid, at the age of 20. *T. Ze.* died of typhoid, at the age of 17.

In this family, there were 22 afflicted members, 8 of whom were females and 14 were males.

VI. C. Ze. is the young member of this family who has recently developed paraparesis and whose clinical studies are reported here. *V Al. Ze.* is the subject of our neuropathologic study.

still run but with some difficulty. He claimed having more difficulty in going downstairs than up. About four years before this he began to have an aching pain behind his knees and in his calves. This had occurred intermittently to date. For a few years he had noted a little dribbling of urine at the end of urination, and in the mornings, at the accustomed time, he would have to hurry to the bathroom for defecation or he would soil himself.

His difficulty in walking had seemed to progress gradually. But he was still able to carry on his work as a drill-press operator.

Neurologic Examination.—The cranial nerves were unaltered. The patient's gait was spastic in type, with a tendency to drag his left lower extremity more than his right. Slight ataxia seemed evident in his gait at times. In the Romberg position he did not sway. Except for a slight ataxia on doing the heel-to-knee test on the right, there was no dysmetria, dyssynergia, or dysdiadokokinesia. Muscle power was definitely impaired in his lower extremities, being more evident in the proximal musculature. There was increased tone of the muscles of his lower extremities, especially on the left side. The usual modalities of sensation seemed to be intact throughout, although vibration sense seemed to be impaired in the dorsum of his feet and in his toes. The tendon and periosteal reflexes were equally active in his upper extremities. There was no sign of Hoffmann. Abdominal and cremasteric reflexes were present. The deep reflexes were equally hyperactive in the lower extremities. Bilateral ankle clonus was obtained. He showed signs of Babinski, Chaddock, Gordon, Oppenheim, Rossolimo, Mendel-Bechterew, and Gonda bilaterally.

Laboratory Studies.—Studies done in the Hospital of the University of Pennsylvania from July 26 to Aug. 7, 1953, revealed the following: hemoglobin of 98%; 5,100,000 erythrocytes per cubic millimeter of blood, and 4100 leucocytes per cubic millimeter of blood, of which 55% were polymorphonuclear leucocytes, 39% were lymphocytes, and 6% were monocytes. Blood urea nitrogen was 15 mg. per 100 cc. Fasting blood sugar was 73 mg. per 100 cc. Urinalysis was essentially negative. Blood serum Kolmer and Kline tests were nonreactive. Gastric analysis showed the presence of free hydrochloric acid. Cerebrospinal fluid was under a pressure of 130 mm. of water. The Queckenstedt test revealed no block of the spinal subarachnoid space. The spinal fluid was clear and contained a few erythrocytes and a protein of 38 mg. per 100 cc. The Kolmer test of the cerebrospinal fluid was nonreactive, and the colloidal mastic test was negative.

Roentgenograms of his chest and entire spine revealed nothing unusual. A myelogram disclosed no obstruction of the entire spinal subarachnoid space.

Report of Neuropathologic Study

Al Ze. (recorded as F. Ze. in the previous report[1]) was born in 1895 and began to have trouble in walking when he was 18 years of age. He continued to have progressive weakness and spasticity of his lower extremities until, finally, he could get around only in a wheel chair.

When he was examined in 1942, his right pupil was smaller than his left, but both pupils reacted well to light and in accommodation-convergence. He was said to have had an intention tremor of both hands, more pronounced on the left side. A moderate degree of disturbance of synergy was noted in the movements of his upper extremities. He had a paraplegia. There was marked spasticity of the muscles of his lower extremities, most prominent in the flexor muscles. Muscle power and tone were intact in his upper extremities. There was no evidence of muscle wasting. There were no fasciculations, and no abnormal involuntary movements. All modalities of sensation were intact throughout. In his upper extremities, the tendon

and periosteal reflexes were equally hyperactive, with a bilateral sign of Hoffmann. The deep reflexes were equally hyperactive in his lower extremities, with bilateral signs of Babinski and Chaddock. Ankle clonus was present bilaterally. Some induration and discoloration of the skin of his legs and feet were present.

The blood serum syphilitic tests were nonreactive. A complete blood cell count was within normal limits.

He was admitted to the Allentown General Hospital, Allentown, Pa., on Dec. 8, 1951. Gradually, over the years, the patient had developed a paraplegia-in-flexion and contractures of the flexor muscles of his thighs. He had become incontinent for urine and feces. He had developed decubitus ulcers of his sacrum and thighs. On admission to the hospital, he was febrile and obviously ill.

A blood count showed a hemoglobin of 54%; 3,060,000 erythrocytes per cubic millimeter of blood, and 12,300 leucocytes per cubic millimeter of blood, of which 84% were neutrophiles, 12% were lymphocytes, 1% were monocytes, and 3% were eosinphiles. No malarial plasmodia were found. A blood culture was sterile. The urine culture showed Proteus vulgaris, as did the cultures of the pus from the bed sores. Blood serum syphilitic tests were nonreactive.

On Jan. 10, 1952, while quite febrile, the patient was seen by one of us (G. A. S.) and was found to be mentally confused, though conscious, and hence poorly cooperative and unreliable. There was no papilledema. His pupils were equal and regular and reacted well to light. His eyeballs moved fully, and there was no nystagmus. His facial muscles moved equally well. Pinprick was apparently perceived throughout. His mental state excluded any reliable assessment of the other modalities of sensation. The patient could move his upper extremities well, but he was generally weak. It was not possible to carry out tests for nonequilibratory coordination with any accuracy. He had a paraplegia-in-flexion, with marked adductor spasm. There were contractures of the flexor muscles of both thighs and both legs. The deep and periosteal reflexes were hyperactive, but equal, in his upper extremities with a bilateral sign of Hoffmann. His abdominal reflexes were absent. His knee jerks were equally hyperactive. Ankle clonus was present bilaterally. The signs of Rossolimo and Babinski, with the usual confirmatories, were present bilaterally.

Despite appropriate therapy and a declining fever, the patient quietly died on Jan. 30.

Dr. Charles Wenner found in the general pathologic examination arteriosclerosis of the spleen, lobular pneumonia, early fatty change of the liver, and arteriosclerotic nephrosclerosis.

The brain and spinal cord were removed about four hours after death and were fixed in formalin. The gross appearance of these structures seemed not unusual.

Blocks of various portions of the nervous system were embedded in celloidin or paraffin or were sectioned frozen. Various stains were utilized—thionine, hematoxylin and eosin, phosphotungstic acid-hematoxylin, Weil's myelin stain, Bodian's silver protein (protargol) stain, and several silver stains.

Spinal Cord (Weil's myelin stain; Fig. 3).—Second Sacral Level: The anterior and posterior columns showed a few scattered swollen fibers. The superficial dorsal portions of the lateral columns showed loss of fibers. In the demyelinated areas there were many swollen fibers and many intact nerve fibers.

Third Lumbar Level: The anterior columns were relatively well preserved, although here there was a loss and swelling of the myelinated fibers lying along the anterior rim. The lateral columns also presented a rim demyelination and swelling of fiber sheaths. In the posterior portions of the lateral columns, there was a triangular area of marked loss of myelinated fibers on each side. These changed areas were located fairly superficially at this level. The devastated areas contained small myelinated fibers and some swollen myelin sheaths. Little change was evident in the posterior columns—a few swollen sheaths and possibly a diffuse loss of fibers.

Twelfth Thoracic Level: The anterior funiculi were essentially intact. Marginal demyelination was evident, starting just inside the anterior curve of the anterior funiculi and continuing around the edge, gradually getting wider toward the lateral columns. Along the gray matter bordering the lateral columns the myelinated fibers were well preserved. As one went dorsad, the subpial change became severer and extended deeper. In the posterior portion of each lateral column was a triangular area of marked demyelination. In these devastated areas there remained a few small myelinated fibers and some swollen sheaths. In the posterior columns, in the midline, and near the posterior commissure was an area of loss of myelinated fibers.

Ninth Thoracic Level: Rim demyelination was noted along the anterior border of the anterior columns near the anterior spinal fissure. There was demyelination along the rim borders of the lateral funiculi. This widened dorsad into the deep triangular area of most intense demyelination, in the posterior part of the lateral columns. In this area few myelinated fibers remained. In the posterior columns the fibers of the columns of Goll seemed thinned; but adjacent to the dorsal medial sulcus and deep within Goll's columns there was an oval area of more intense demyelination.

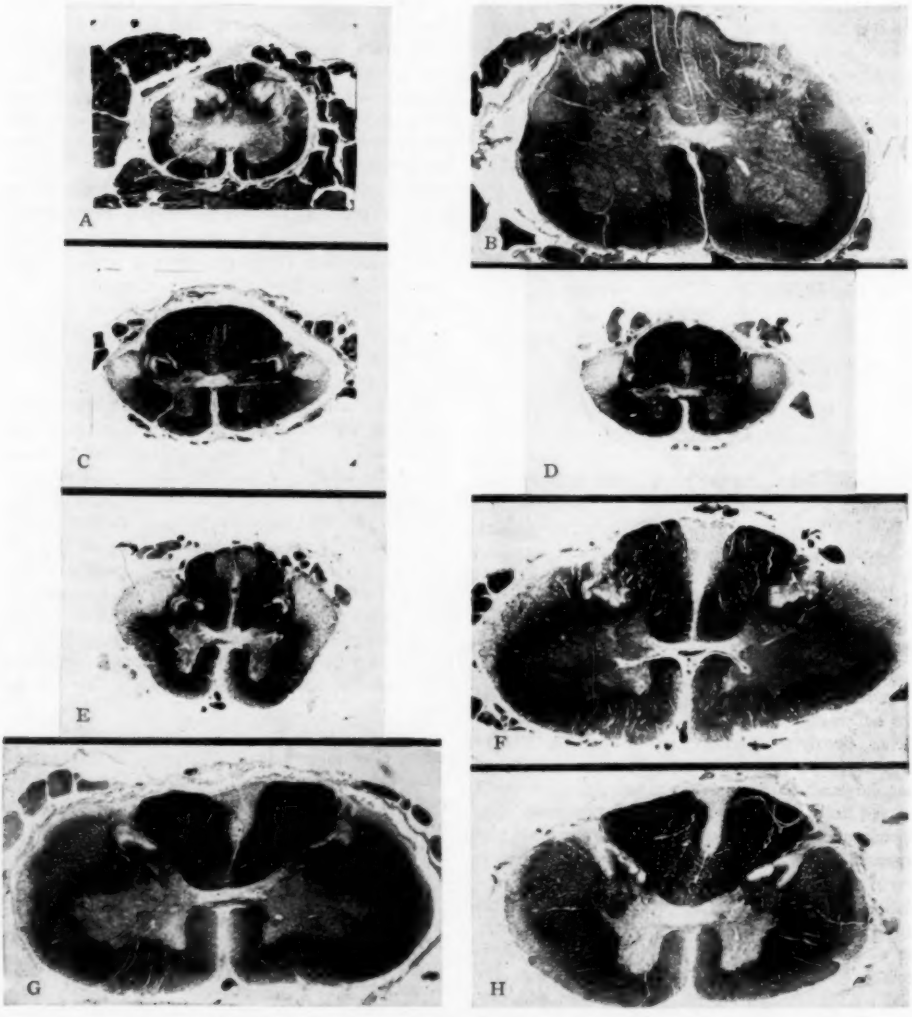


Fig. 3.—Spinal cord. *A*, 2d sacral level; *B*, 3d lumbar level; *C*, 12th thoracic level; *D*, 9th thoracic level; *E*, 2d thoracic level; *F*, 8th cervical level; *G*, 5th cervical level; *H*, 3d cervical level. Weil's stain for myelin. Reduced to 45% of mag. × 10.

Second Thoracic Level: In the anterior columns rim demyelination was again evident, being more pronounced on one side. In these areas, some nerve fibers seemed to be lost and some remaining fibers were swollen. This same peripheral myelin thinning was evident in the lateral columns. Dorsal to the level of the lateral horns a deep triangular area of intense demyelination was encountered. The destruction extended to the ground bundle area, which was intact, and to the posterior root zone, which was also intact. In the damaged areas a few myelinated fibers remained. The columns of Goll showed a spotty demyelination. The loss of fibers seemed to be more evident deep within Goll's columns, with preservation of the fibers in the inner third and along the dorsal intermediate septum, especially in its deeper portions.

Eighth Cervical Level: Along the inner lip of the anterior column on one side there was a slight thinning of fibers at the surface of the cord. A narrow rim of fiber thinning extended from the anterior columns into the lateral columns. At about the level of the nucleus motorius lateralis, the border area of myelin loss began to deepen; and in

the posterior part of the lateral columns this extended into a deep triangular area of severe fiber loss. In the demyelinated triangular areas the greater loss of fibers seemed to be peripheral; many well-preserved sheaths remained, and there were some swollen, thinned sheaths. In the posterior funiculi, the wide columns of Burdach were intact. Goll's columns showed a spotty demyelination in a roughly triangular area along the posteromedian sulcus. Preserved myelin sheaths and swollen sheaths were scattered throughout this affected area, too.

Fifth Cervical Level: In one of the anterior columns, deep in the anterior spinal fissure, there was an area of loss of myelinated fibers. The anterior rim of the anterior funiculi showed thinning of myelinated fibers and swelling of many myelin sheaths. This thinning continued along the ventrolateral rim of the spinal cord on both sides and deepened at the level of the lateral portion of the anterior horn—actually there was rim degeneration from anterior root zone to posterior root zone. In these thin demyelinated areas intact myelin sheaths were found. There was a rather definite area of demyelination in the posterior part of each lateral column. The area extended roughly in a triangular form, with its base along the periphery of the spinal cord. Definite loss of fibers had occurred here, and many remaining fibers were swollen. Yet the destruction here seemed less than along the rim. In the posterior columns, a triangular area of demyelination was noted in the midline of the columns of Goll. The area extended a little more than halfway in toward the posterior commissure. The affected area was severely denuded of myelinated fibers, although intact fibers were present in the midst of the devastation.

Second Cervical Level: Along the medial edge of one of the anterior columns, there seemed to be a slight thinning of fibers. In the lateral columns, there was a marked rim demyelination beneath the pia mater. In the posterior part of the lateral columns, the myelin loss was not as marked as below, while in the posterior columns an intense demyelination was evident along the posterior median sulcus. This extended from the surface of the cord about half the distance to the posterior commissure. In the damaged fields, some normal-appearing and some thinned, swollen myelin sheaths remained.

Brain Stem (Weil's myelin stain).—Medulla Oblongata, Level of Decussation of Pyramids (Fig. 4*A*): The pyramids seemed to stain less deeply than expected and contained a few thinned, swollen myelin sheaths. There was marked demyelination of the fibers over the dorsal and medial surfaces of the gracile nuclei. In the demyelinated areas, preserved myelin sheaths were noted, as well as swollen sheaths. Marked demyelination of both dorsal

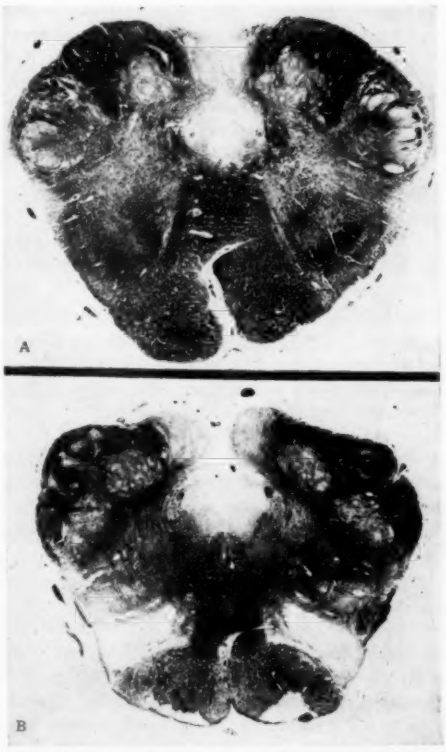


Fig. 4.—Medulla oblongata. *A*, level of decussation of pyramids. Note the integrity of the pyramidal fibers, and the demyelination of Flechsig's tracts and about the gracile nuclei. *B*, level of inferior olivary bodies. Note the preserved, but small, pyramids. Weil's stain for myelin. Reduced to about 47% of mag. × 10.

spinocerebellar tracts was very evident, but here, too, preserved and swollen sheaths were evident in the demyelinated areas. Similar, but less severe, change was noted in the ventral spinocerebellar tracts.

Medulla Oblongata, Level of the Inferior Olivary Bodies (Fig. 4*B*): Little change was apparent at this level. It was not possible to trace the spinocerebellar tracts into the restiform bodies as distinct demyelinated tracts. What was more surprising was the normal appearance of the pyramids at this level!

Mesencephalon: We especially studied the cerebral peduncles, but no consistent changes were evident.

Quantity and Size of Myelinated Sheaths in the Pyramids: Following the technique described by Lassek,[24] we measured and counted the myelinated fibers in one pyramid just above its decussation in

the medulla oblongata. The area of this pyramid was 5.87 sq. mm., as determined from a camera-lucida drawing measured by the planimeter. We counted and measured the diameters of 37,581 myelin sheaths from various portions of this pyramid. These fibers were found to occupy an area of 0.5866 sq. mm. The calculated total number of myelinated nerve fibers in this one pyramid was 376,055. Of the 37,581 fibers which we measured, 33,465, or 89%, were small fibers (1μ to 4μ in diameter); 3,307, or 8.8%, were medium-sized fibers (5μ-10μ in diameter), and 809, or 2.2%, were large fibers (11μ or larger).

Spinal Cord (hematoxylin and eosin stain).—The roots of the cauda equina and their blood vessels presented no change. Around the rim of the spinal cord, just beneath the pia mater, were structureless globules which stained a light or purplish blue. They were round bodies and were arranged three or four deep at the edge of the spinal cord. Similar bodies were scattered irregularly about the white matter of the cord. They were more abundant in the posterior part of the lateral columns and in Goll's columns.

At the 12th thoracic level, the posterior columns and the posterior part of the lateral columns had a loose appearance reminiscent of status spongiosus. The spinal cord seemed smaller in the upper thoracic levels. One of the striking changes in the thoracic cord was the absence of the pink stain of eosin in the dorsal half of both lateral columns and in the middle of the posterior columns. In the pale areas (which were coextensive with the demyelinated areas described in the Weil-stained sections), the neurokeratin frameworks were gone; axis cylinders were not seen, and the background was a fine, nonstaining, fibrinogranular structure with many small vessels and an increased number of nuclei. The nuclei seemed to be those of astrocytes, oligodendrocytes, and a few microglia cells.

Brain Stem (hematoxylin and eosin stain).—Medulla Oblongata, Level of Decussation of Pyramids: Poor eosin staining was noted in an area medial and dorsal to the gracile nucleus on both sides and in both dorsal spinocerebellar tracts. In these pale areas, nuclei were increased and neural elements poorly identified.

Spinal Cord (thionine stain).—No changes were noted in the neurones other than the large accumulations of granular pigment in the cytoplasm of the anterior horn cells. The neurones in the posterior horns were readily identified. A few intact neurones were observed in the region of Stilling's column. The corpora amylacea stained a pale blue with this stain and were most abundantly located at the periphery of the cord, especially of the lateral and posterior funiculi.

It was noted that there were no large neurones in the dorsal nuclei of Clarke. The autonomic neurones of the lateral horns were not changed.

Spinal Cord (scarlet red [Sudan IV] counterstained with Mayer's hematoxylin).—At all levels, most of the anterior horn cells showed single masses of a granular, orange-colored material occupying one position in the cytoplasm. The rest of the cytoplasm, the nucleus, and the nucleolus of each neurone stained blue. The demyelinated areas in the lateral and posterior columns showed no fat but did show blue-staining corpora amylacea.

Spinal Cord (Phosphotungstic acid-hematoxylin stain).—With this stain, the demyelinated areas in the lateral and posterior columns were as plainly seen as with the myelin stain. In the demyelinated areas the septal and perivascular collagen seemed to be increased and denser. Scattered throughout these areas were many fine, blue-staining fibrils, which were wavy and delicate and often ran perpendicular to the longitudinal axis of the spinal cord. At some levels these areas had a spongy appearance. They always appeared quite cellular. Generally, the demyelinated areas consisted of a loose pink, amorphous background, a few myelinated fibers, many small blood vessels with prominent collagenous walls, many nuclei, many wavy blue fibrils, and increased septal collagen fibers.

Medulla Oblongata (phosphotungstic acid-hematoxylin stain).—In the lower medulla, demyelination of the dorsal spinocerebellar tracts and of the gracile fascicles was well demonstrated by this stain, but without the changes noted in the cord. In the upper medulla no abnormalities were noted.

Spinal Cord (Hortega's silver carbonate stain for connective tissue and blood vessels).—The corpora amylacea stained a homogeneous black and were most abundant beneath the pia mater and along the blood vessels. They were more abundant in the demyelinated, denervated areas and in the upper thoracic portion of the spinal cord.

In the posterior portions of the lateral columns and the medial portions of the posterior columns in the upper thoracic region, and in the medial portions of the posterior columns in the cervical region, the fibrils in the walls of the blood vessels were increased. This was particularly evident in the vessels penetrating from the surface of the cord.

Spinal Cord (sodium perborate and ammonium-silver nitrate stain for nerve fibers).—In the lumbar level, little change was apparent in the posterior columns, but in the posterior part of the lateral columns there were fewer large nerve fibers, although many small ones remained.

In the thoracic levels, the axis cylinders were markedly reduced in number in the posterior portions of the lateral columns. Practically no large fibers were noted. Only a few small fibers remained. The remaining fibers were scattered spar-

ingly in the destroyed areas. The blood vessels seemed to be especially prominent in the affected areas. A similar, but less marked, change was noted along the midline of the posterior columns.

In the cervical levels, changes in the columns of Goll were more evident. Here were seen loss of most axis cylinders, but preservation of some, a granular ground substance, and the corpora amylacea. The posterior parts of the lateral columns presented less severe change at these levels, the greatest effect being apparent near the surface of the cord. In the corticospinal tracts, many large nerve fibers were visible among the more numerous small ones.

Left Motor Cortex.—After fixation in formalin, the left central region (Areas 6, 4, 3, 1, and 2 of Brodmann) was removed en bloc, cut into smaller portions, embedded in celloidin, and cut serially at 35μ. Every 10th section was stained with thionine. We then measured and counted the giant pyramidal cells of Betz. All cells included in our study were located in Lamina V. The borders of the neurones in this area were outlined with the camera lucida and measured with the planimeter. We calculated the areas of these cells in square microns. We counted only those cells in which the nucleoli were discernible. After calculating cell area, we allowed 30% for shrinkage. We actually measured 5811 cells. Following Lassek,[25] we have included as Betz cells only those neurones whose area was 900 sq. μ or more. In this manner, we arrived at the conclusion that there were 23,652 Betz cells in the left motor area of our patient.

It was noted that the adjacent premotor area and postcentral gyrus showed no neuronal changes of significance. A very occasional Betz cell showed early chromatolysis, but there was no consistent pathology of these neurones.

COMMENT

The pathology of the nervous system in hereditary spastic paraplegia may be said to rest upon the necropsy findings of seven cases reported by Strümpell (two cases),‖ Newmark (three cases),¶ Jakob,[32] and Kahlstorf.[33] The reasons for separating these few cases from others in the literature has been discussed fully previously.[1] The pathologic findings can be summarized as follows: (1) Demyelination and destruction of axis cylinders in both lateral corticospinal tracts, chiefly in the thoracic portions of the spinal cord and less in the upper cervical levels, in all seven cases. (2) Demyelination of the ventral corticospinal tracts, always less severe, in four cases. (3) Symmetrical bilateral demyelination of the spinocerebellar tracts, in four cases. (4) Bilateral symmetrical demyelination of the fasciculus gracilis, always more evident in the cervical levels, in all seven cases. (5) Number of neurones of Clarke's columns diminished, in two cases. (6) Number of anterior horn cells diminished, in one case. (7) Minor changes in the cerebellum, basal ganglia, and rubrospinal tract, in one case. (8) Changes in the internal capsule, cerebral peduncles, pons, or medulla, in only one case. (9) Betz cells atrophic or judged to be reduced in number, in three cases.

Thus, in hereditary spastic paraplegia the major pathologic changes seem to have been found in the spinal cord. Furthermore, the most conspicuous changes occurred in the lower cervical and upper thoracic portions of the spinal cord. Above the upper thoracic region the columns of Goll were most degenerated, and below the lower cervical level the lateral corticospinal tracts were most involved. Bilateral, symmetrical involvement was the rule.

The spinal cord of our patient revealed the following significant changes: (1) demyelination and loss of most of the axis cylinders of both crossed corticospinal tracts, more evident below the midcervical level and most extensive in the thoracic levels; (2) demyelination and loss of axis cylinders of both dorsal spinocerebellar tracts of Flechsig, traceable into the medulla oblongata; (3) demyelination and loss of axis cylinders of the medial portions of the columns of Goll upward from the lowest thoracic level, most marked in the upper cervical level and traceable to the gracile nuclei in the medulla oblongata, and (4) marked loss of neurones in the dorsal nuclei of Clarke.

Thus, our case showed spinal cord findings fairly consistent with those previously reported. There was no clear-cut involvement of the ventral (direct, or uncrossed) corticospinal tracts in our patient. There was a rim fiber swelling, and perhaps fiber thinning, which was felt to have no special pathologic

‖ References 26 and 27.

¶ References 28 to 31.

significance. The involvement of the ventral spinocerebellar tracts of Gowers was uncertain; while it was suggested in the thoracic levels, we could not follow the changes consistently throughout the known extent of this tract.

It might be appropriate to consider here the nature of the pathologic change in the spinal cord as far as that can be gleamed from the histologic examination. Besides the loss of myelin sheaths and disappearance of axon cylinders, the devastated areas in the cord and in the medulla showed the following fairly consistent findings: spotty persistence of myelin sheaths and axis cylinders, hypercellularity because of increased number of astrocytes and oligodendrocytes, hypervascularity with fibrillar thickening of vessel walls, a loose fibrillar gliosis, and abundant corpora amylacea. Of all the possible processes, these changes would seem best to fit into that vague category called "degenerative diseases."

Our first studies of the pyramidal tracts above the spinal cord levels showed no apparent involvement, for there was no obvious demyelination of the pyramids and no fiber loss apparent in the cerebral peduncles. Then, too, the cells of Betz revealed no chromatolysis or other pathologic change. So it was that we decided to attempt a quantitative study of the neurones and nerve fibers of the motor system above the spinal cord level.

The nerve fibers of the pyramidal tracts are most readily examined in the pyramids of the medulla oblongata. The size of a pyramid just above the decussation was found by Duncan [34] to vary from 8.16 to 13.7 sq. mm. in 128 specimens. Lassek [24] found the area of one pyramid of a 20-year-old Negro man to be 11.31 sq. mm. and that of an 18-year-old Negro woman to be 11.96 sq. mm. Lassek [35] found the areas of the pyramidal tracts just above the motor decussation at different ages to vary as follows: newborn infant, 1.89 sq. mm.; 1 month, 2.75 sq. mm.; 3 months, 2.18 sq. mm.; 8 months, 2.98 sq. mm.; 11 months, 5.43 sq. mm.; 2 years, 5.83 sq. mm.; 22 years, 11.71 sq. mm., and 80 years, 7.25 sq. mm. (shrinkage was computed at 30%).

Our patient's pyramid measured 5.87 sq. mm. (actual size; shrinkage not computed). Our patient died at the age of 57. Using the figures of Duncan [34] and Lassek # as normal controls, it is apparent that the area of the pyramid of our patient was definitely smaller than normal. Indeed, it was smaller than the lowest value mentioned by Duncan [34] and smaller than the reduced area associated with age as observed by Lassek.[35] The pyramid of our patient could be said to be little larger than that of a 2-year-old child!

The total number of nerve fibers in the pyramid next attracted our attention. Lassek [24] counted the number of myelinated fibers in the human pyramid just above the pyramidal decussation in two specimens. He calculated that there were 625,700 myelinated nerve fibers in one pyramid of the 20-year-old Negro man and 752,000 myelinated nerve fibers in one pyramid of the 18-year-old Negro woman.

We estimated that there were 376,055 myelinated nerve fibers in one pyramid of our patient. Thus, here again, we found a marked reduction in the total number of nerve fibers in the pyramid of our case if we used Lassek's [24] values as indicating the normal quantity. Yet microscopically the pyramid gave no indication of such a loss of fibers in its low-power appearance (Fig. 4).

We next turned to a study of the size of the nerve fiber population of the pyramid. Lassek [24] had measured the diameters of the myelin sheaths of 30,000 nerve fibers in the pyramid just above the motor decussation in the medulla of his two young adults. He found that 89.57% measured 1μ to 4μ in diameter, 8.7% measured 5μ to 10μ in diameter, and only 1.73% measured 11μ or more in diameter.

In our patient, we measured the diameters of 37,581 myelinated nerve fibers in the pyramid just above the decussation and found that 89% were 1μ to 4μ in diameter, 8.8% were 5μ to 10μ in diameter, and 2.2% were

References 24 and 35.

11μ or more in diameter. Thus, here our findings most closely approximated the normal control values obtained by Lassek.[24] It would seem to indicate that the loss of nerve fibers in the pyramid of our patient included all sizes of fibers, so that those that remained were of the "normal" size distribution. Thus, the lost fibers included many others than the large fibers, which are presumed to represent the axons of the Betz cells.

We had found no obvious change in the nerve fibers of the cerebral peduncles, and so we decided to count or carefully estimate the Betz cells in the motor area of one cerebral hemisphere. Campbell [26] had estimated that there were 25,000 cells of Betz in each motor area. He had counted every fifth slide of his serial sections. Lassek [25] objected to this, as well as to the fact that Campbell had not indicated any specifications for recognition of Betz cells. Lassek,[25] therefore, defined the kind of neurons he meant as the Betz cell as follows:

> The cell must be situated in the infragranular layer of the motor area of the cortex, be large and pyriform, possess abundant tigroid material, which has a marked affinity for the stain and, finally, have a spherical nucleus which is small in proportion to the size of the cell body.

He included all such cells "between 900 and 4,000 square microns in area, shrinkage being taken into account." Lassek counted the nucleoli of such cells seriatim. He found 34,562 Betz cells in the left motor area and 34,183 Betz cells in the right motor area of the cerebral hemispheres of a 22-year-old Negro woman.

Following the technique and criteria established by Lassek,[25] we counted the nucleoli of the neurons located in the fifth lamina and below the internal granular layer, and whose cell area measured over 900 sq. μ, allowing for shrinkage, of Area 4 of the left cerebral hemisphere of our patient. We studied only every 10th section, but we drew and measured the area of every such cell in these sections. We then calculated the number of Betz cells in the left motor area and found them to be 23,652. Here, again, if one takes Lassek's figures as representing the most accurate normal control values available, it would seem there was indeed a loss of these large neurons from the motor area of our patient.

In previous reports,* the impression had been expressed that there were fewer Betz cells in the paracentral lobule. Since this area purportedly contains the motor supply for the lower extremities and since the chief feature of this syndrome is a spastic weakness of the lower extremities, a careful evaluation of the neurons in this area seemed indicated. Lassek [25] had found 75.5% of the Betz cells to be in the upper third of the motor cortex, 17.9% in the middle third, and 6.6% in the lower third. We did not feel so freely about dividing the cerebral motor strip into three areas, for we found no Betz cells in a considerable portion of the precentral gyrus immediately dorsal to the Sylvian fissure. Most of the cells we found distributed in the dorsal portion of the precentral gyrus and in the paracentral lobule, so that a decision as to which is leg, arm, or face area seemed indeterminable on histologic grounds alone.

Thus, a quantitative study of certain portions of the motor system in our patient revealed evidence suggesting that there was a loss of nerve fibers and neurones of this system above the level of the spinal cord where obvious changes had been observed. There would seem to be a reduction in the number of Betz cells in the motor cortex and a loss of fibers in the pyramids of the medulla oblongata. But certainly this is not a disease process limited only to the Betz cells and their axons, for if this were so the fiber size of the pyramids should contain an unusually large proportion of small or medium-sized fibers. Actually, the remaining fibers of the medullary pyramid of our patient were of the size distribution described by Lassek [24] for the normal. Large, small, and medium-sized fibers were lost proportionately in our case. The origin of these fibers is uncertain, so that little can be gleaned

* References 28 and 29.

from these findings alone as to the locus of the disease process.

The problem as to whether the pathologic process in hereditary (familial) spastic paraplegia mainly falls upon the spinal cord or above this level has bothered many students of this illness. For instance, in an attempt to resolve this problem, Appel [7] emphasized the clinical observations that early in the course of the illness the spasticity of the muscles of the lower extremities is often noted first and remains more marked than the loss of power for a long time (also stressed by André-Thomas and associates [8]). Also, early in the illness, the Babinski sign may be absent and the abdominal reflexes may be preserved. He felt that such early cases presented a clinical picture that most closely resembled the syndrome produced experimentally in animals by Fulton and his co-workers [37] when they extirpated Area 6 of Brodmann. Appel felt that Schaffer's † findings of neuronal changes in Layers III and IV of the precentral gyri in his two cases strengthened this idea. He concluded that in hereditary (familial) spastic paraplegia the pathologic process affected first the cortical cell bodies that control the physiology of Area 6. We were unable to find any obvious changes in the neurones of Brodmann's cortical Areas 6 and 8 in our patient.

Another viewpoint has been expressed by Kinnier Wilson,[40] when he spoke of the pathologic process of hereditary (familial) spastic paraplegia as occurring in a "cortico-distal" or "nucleo-distal" fashion, i. e., "degeneration beginning farthest away from trophic centres." Greenfield [41] has suggested a similar idea about the spinocerebellar degenerations, of which he said, "The pathological process appears to be a slow or more rapid dying back of the neurones in certain systems from the periphery to the centre with eventual disappearance of the cell body." More specifically, both Wilson and Greenfield base their explanations on the authoritative Gowers' "abiotrophy"—"a slow decay of the nerve elements which have a common function, a decay limited to these but extending throughout their entire extent." [41]

From the available data, it would seem to us that the major locus of pathologic effect in hereditary (familial) spastic paraplegia might be in the thoracic portion of the spinal cord. This would explain the demyelination of Goll's columns, best seen in the cervical cord and medulla, and the fiber loss of the dorsal spinocerebellar tracts, best seen in the thoracic and cervical cord and the lower medulla. The loss of Betz cells in the cortex of our patient would seem to us to be the result of retrograde degeneration—an occurrence frequently encountered following chronic fiber destruction in the brain and spinal cord, as Lassek has reiterated.[42] The smallness of the medullary pyramids and the proportionate loss of nerve fibers in these structures would seem to us to be also an expression of retrograde degeneration within the neuraxis, occurring so gradually, over so many years, in our patient that the medullary pyramids seemed to have adapted by simply reducing in size and hence microscopically appearing to be intact.

The nature of the pathologic process in this heredofamilial disease remains obscure. There has been nothing observed histologically in the cases in the literature to explain this phase of the problem, and none was forthcoming from our present study. While it has been presumed that some sort of a susceptibility of certain pathways of the central nervous system may be inherited in these families, there would seem to be at least the possibility that the defect may not be neural, but, rather, elsewhere in the body, albeit acting at this neural level. No metabolic or toxic factor has ever been disclosed.

One of the difficulties in the clinicopathologic correlations in hereditary (familial) spastic paraplegia has been the destruction of Goll's columns and the failure to find clinical evidence of loss or impairment of posterior column functions in the lower extremities of patients suffering from this illness. Newmark † had observed this discrepancy years ago. In our patient, Al. Ze., one unfortunately could not evaluate vibration

† References 28 to 31.

sense and position sense in his lower extremities during his premortem illness because of the toxidelirious state. However, his brother, M. Ze., has been reexamined several times in the past few years by one of us (June 18, 1953, and Aug. 5, 1954). This man has had urinary and defecatory troubles for at least 10 years in the form of urgency and occasional incontinence of urine, nocturia, and urgency of defecation, gradually getting worse. He was able to get about with a cane until five years ago. When last seen, he was only able to sit up in his wheel chair. His right leg could not be extended beyond a right angle on his thigh, though he could extend his left leg almost fully. There was severe weakness or paralysis of the muscles of his lower limbs, more marked distally—for instance, he was unable to move his toes or feet on either side. His tendon and periosteal reflexes were a little more active in the left upper extremity. There was a Hoffmann sign on the left. His left lower abdominal reflex was obtained. His knee jerks were hyperactive. He showed bilateral ankle clonus and signs of Babinski and Rossolimo. His sensory responses have been a little inconsistent from time to time; however, in general, one got the impression that touch, pain, and temperature perception were impaired in both legs and feet. Position sense seemed markedly impaired in both large toes, although it was not absent. Vibration sense did seem to be absent in the legs and feet, but occasionally awareness of vibration was demonstrated in the large toes. Thus, it may be that in the very late stages of this illness, sensory changes may occur in the lower extremities—after all, this man has had his illness for over 50 years.

SUMMARY

The clinical findings of a new family with hereditary (familial) spastic paraplegia are recorded.

The clinical findings in a new case of the previously reported Family Ze. are described.

In the spinal cord of a member of the Ze. family, we noted demyelination and loss of axis cylinders of both crossed corticospinal tracts, evident below the midcervical level and most marked in the thoracic levels; of both dorsal spinocerebellar tracts, traceable into the medulla oblongata; of the columns of Goll upward from the lower thoracic levels, and most marked in the upper cervical level and traceable to the gracile nuclei in the medulla, and loss of the neurones in the dorsal nuclei of Clarke. Quantitatively determined, our case also showed smaller-than-normal pyramids, a less-than-normal number of nerve fibers in the pyramids, and a smaller-than-normal number of Betz cells in the motor cortex.

The significance of these findings is discussed from the viewpoint of pathogenesis.

REFERENCES

1. Schwarz, G. A.: Hereditary (Familial) Spastic Paraplegia, A. M. A. Arch. Neurol. & Psychiat. **68**:655-682, 1952.

2. Rhein, J. H. W.: Family Spastic Paralysis, J. Nerv. & Ment. Dis. **44**:115-144; 224-242, 1916.

3. Paskind, H. A., and Stone, T. T.: Familial Spastic Paralysis: Report of 3 Cases in One Family and Observation at Necropsy, Arch. Neurol. & Psychiat. **30**:481-500, 1933.

4. Price, G. E.: Familial Lateral Sclerosis (Spastic Paralysis), J. Nerv. & Ment. Dis. **90**:51-55, 1939.

5. Bell, J., and Carmichael, E. A.: On Hereditary Ataxia and Spastic Paraplegia, in Bell, G., and Carmichael, E. A.: Treasury of Human Inheritance, London, Cambridge University Press, 1939, Vol. 4, Pt. 3.

6. Seeligmüller, A.: Sklerose der Seitenstrange des Rückenmarks bei 4 Kindern derselben Familie, Deutsche med. Wchnschr. **2**:185-186, 1876.

7. Appel, L.: Études sur la paraplégie spasmodique familiale analogie avec le syndrome de l'aréa 6, Acta neurol. et psychiat. belg. **49**:415-432, 1949.

8. André-Thomas, J.; Ajuriaguerra, J., and Vargues, R.: Les troubles du tonus musculaire dans la paraplégie spasmodique familiale, Rev. neurol. **82**:198-204, 1950.

9. Garland, H. G., and Astley, C. E.: Hereditary Spastic Paraplegia with Amyotrophy and Pes Cavus, J. Neurol. Neurosurg. & Psychiat. **13**:130-133, 1950.

10. Curcio, F. I.: Enfermedad de Strümpell-Lorrain, Prensa méd. argent. **37**:331-335, 1950.

11. Alajouanine, T., and Nick, J.: Paraplégie spasmodique familiale avec troubles cérébelleux et paralysie verticale du regard (présentation de deux frères), Rev. neurol. **84**:182-185, 1951.

12. Appel, L., and van Bogaert, L.: Études sur la paraplégie spasmodique familiale: II. La famille Amiel: formes très précoces et congénitales. Contribution histopathologique, Acta neurol. et psychiat. belg. **51**:129-166, 1951.

13. Appel, L., and van Bogaert, L.: Études sur la paraplégie spasmodique familiale: III. La famille Tib. . .: formes très précoces de la paraplégie spasmodique familiale avec idiotie et oligophrénie dans les branches collatérales, Acta neurol. et psychiat. belg. **51**:716-730, 1951.

14. Landau, W. M., and Gitt, J. J.: Hereditary Spastic Paraplegia and Hereditary Ataxia: A Family Demonstrating a Variety of Phenotypic Manifestations, A. M. A. Arch. Neurol. & Psychiat. **66**:346-354, 1951.

15. Michaux, L.; Teysseyre, J., and Fandre, M.: Paraplégie spasmodique familiale de type Strümpell-Lorrain, Arch. franç. pédiat. **9**:59-61, 1952.

16. Heuyer, Lebovici, and Seignot: Paraplégia spasmodique familiale avec affaiblissement intellectuel chez deux sœurs: maladie de Schilder, Arch. franç. pédiat. **9**:62-65, 1952.

17. Aceto, G.: Contributo alla conoscenza del morbo di Strümpell, Minerva pediat. **4**:491-494, 1952.

18. Appel, L., and van Bogaert, L.: Études sur la paraplégia spasmodique familiale: IV. La famille Fev. . . : forme très tardive. Contribution histopathologique, Acta neurol. et psychiat. belg. **52**:129-140, 1952.

19. van Bogaert, L.: Études sur la paraplégie spasmodique familial: V. La famille van L. . . forme classique pure avec atrophic optique massive chez certains de ses membres. Considérations génétiques sur la paraplégie spasmodique familiale en général, Acta neurol. et psychiat. belg. **52**:795-807, 1952.

20. van Bogaert, L.: Étude génétique sur les paraplégies spasmodiques familiales, J. génét. humaine **1**:6-23, 1952.

21. Nayrac, P., and Warot, P.: Paraplégie spasmodique familiale chez deux sœurs, Écho méd. Nord **24**:266-269, 1953.

22. Dick, A. P., and Stevenson, C. J.: Hereditary Spastic Paraplegia: Report of a Family with Associated Extrapyramidal Signs, Lancet **1**:921-923, 1953.

23. Refsum, S., and Skillicorn, S. A.: Amyotrophic Familial Spastic Paraplegia, Neurology **4**: 40-47, 1954.

24. Lassek, A. M.: The Human Pyramidal Tract: IV. A Study of the Mature, Myelinated Fibers of the Pyramid, J. Comp. Neurol. **76**:217-225, 1942.

25. Lassek, A. M.: The Human Pyramidal Tract: II. A Numerical Investigation of the Betz Cells of the Motor Area, Arch. Neurol. & Psychiat. **44**: 718-724, 1940.

26. Strümpell, A.: Über eine bestimmte Form der primären combinirten Systemerkrankung des Rückenmarks, im Anschluss an einen Fall von spastischer Spinalparalyse mit vorherrshender Degeneration der Pyramidenbahnen und geringerer Betheiligung der Kleinhirn-Seitenstrangbahnen und der Goll'schen Stränge, Arch. Psychiat. **17**:227-238, 1886.

27. Strümpell, A.: Die primäre Seitenstrangsklerose (spastische Spinalparalyse), Deutsche Ztschr. Nervenh. **27**:291-339, 1904.

28. Newmark, L.: A Contribution to the Study of the Family Form of Spastic Paraplegia, Am. J. M. Sc. **105**:432-440, 1893.

29. Newmark, L.: Über die familiäre spastische Paraplegie, Deutsche Ztschr. Nervenh. **27**:1-23, 1904.

30. Newmark, L.: Pathologisch-anatomischer Befund in einem weiteren Falle von familiärer spastischer Paraplegie, Deutsche Ztschr. Nervenh. **31**: 224-230, 1906.

31. Newmark, L.: Klinischer Bericht über den siebenten Fall von spastischer Paraplegie in einer Familie und Ergebnis der dritten Autopsie aus derselben Familie, Deutsche Ztschr. Nervenh. **42**: 419-431, 1911.

32. Jakob, C.: Sobre un caso de paraplegia espasmodica familiar progresiva (maladie de Strümpell) conexamen histopatologico completo, Riv. Soc. méd. argent. **17**:665-703, 1909.

33. Kahlstorf, A.: Klinischer und histopathologischer Beitrag zur hereditären spastischen Spinalparalyse, Ztschr. ges. Neurol. u. Pyschiat. **159**: 774-780, 1937.

34. Duncan, D.: Individual Variations in the Size of the Medullary Pyramids; abstracted, Anat. Rec. **76**:64-65, 1940.

35. Lassek, A. M.: The Human Pyramidal Tract: V. Postnatal Changes in the Axons of the Pyramids, Arch. Neurol. & Psychiat. **47**:422-427, 1942.

36. Campbell, A. W.: Histological Studies on the Localization of Cerebral Function, London, Cambridge University Press, 1905.

37. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1943, Chap. XXI, pp. 394-417.

38. Schaffer, K.: Zur Pathologie und pathologischen Histologie der spastischen Heredo-Degeneration (hereditäre spastische Spinalparalyse), Deutsche Ztschr. Nervenh. **73**:101-128, 1922.

39. Schaffer, K.: Zur Histopathologie der idiotypischen lateral Sklerose oder spastischen Heredodegeneration, Arch. Psychiat. **77**:675-697, 1926.

40. Wilson, S. A. K.: Neurology, Baltimore, The Williams & Wilkins Company, 1940, p. 783.

41. Greenfield, J. G.: The Spino-Cerebellar Degenerations Springfield, Ill., Charles C Thomas, Publisher, 1954, pp. 14 and 17.

42. Lassek, A. M.: The Pyramidal Tract, Springfield, Ill., Charles C Thomas, Publisher, 1954, pp. 36-43.

Alteration of Copper Metabolism in Chlorpromazine-Treated Cases

H. AZIMA, M.D.
and
A. RICHMAN, M.D., Montreal, Canada

The purpose of this paper is to demonstrate that some cases treated with chlorpromazine show alterations of copper metabolism, and a syndrome similar perhaps in some respects to Wilson's disease (hepatolenticular degeneration).

Azima and Ogle,[1] Lehman and Hanrahan,[2] and others have previously reported a 5% incidence of extrapyramidal complications, or what appears to be a Parkinson-like syndrome, in chlorpromazine-treated cases. The development of extrapyramidal signs, and the occurrence of liver damage, which also is found in 5% to 15% of persons treated with chlorpromazine,* led us to the supposition that perhaps the phenomenon represented a hepatolenticular disturbance similar to Wilson's disease. Although the hepatic lesions associated with chlorpromazine therapy appear to be cholangiolitic in nature,[3] whereas in Wilson's disease they are parenchymal, there is no definite evidence that the hepatic lesions in the early stages of Wilson's disease are solely parenchymal, or that the continuation of chlorpromazine in the presence of cholangiolitis will not eventually lead to parenchymal damage.

There has been growing evidence that in Wilson's disease the metabolism of copper is altered.† This study was undertaken to investigate whether there was an alteration of copper metabolism in cases treated with chlorpromazine.

METHOD

A preliminary serial measurement of plasma copper in one patient (Case 24, Table 1), who manifested definite extrapyramidal signs (rigidity, tremor, decrease in associated movements, mask-like facies, etc.) on the first week of chlorpromazine therapy, revealed a gradual, but marked, increase in plasma copper, which returned to a relatively normal level two weeks after the cessation of the treatment. This observation encouraged us to undertake a more systematic study of the problem. For this purpose, the plasma copper of 25 nonselected psychiatric patients (average age of 40) who received chlorpromazine was measured before the treatment and at the end of the first, third, and fifth weeks after the beginning of the treatment. The intervals were chosen in this manner because the previous investigation had shown that the neurological signs usually began to appear after the first week of therapy; the average age of these 25 cases was 40. The control series consisted of 25 cases who received other forms of treatment (electric shock, insulin coma, reserpine [Serpasil], etc.). Their average age was 45.

The chlorpromazine dose varied from 75 to 400 mg. per day. The drug was administered by mouth. Patients were checked periodically for the evidence of neurological signs.

Liver function tests were performed once a week in all patients who received chlorpromazine. These included determinations of alkaline phosphatase, bilirubin, cephalin-cholesterol flocculation, thymol

Received for publication Oct. 3, 1955.

Allan Memorial Institute of Psychiatry and McGill University.

This project was subsidized by a grant from Poulenc, Ltd., of Canada.

Messrs. Jeffrey and Avon, of Poulenc, Ltd., cooperated in this study, and Mrs. H. Berger, of the Allan Memorial Institute, and Miss P. Wood, of the Dr. E. H. Bensley Laboratory at the Montreal General Hospital, gave technical assistance.

* References 1 to 3.

† References 4 to 9.

turbidity and flocculation, total cholesterol, cholesterol esters, total serum protein, and albumin-globulin ratio. The plasma copper was measured by the sodium diethyldithiocarbamate method.[10] In cases in which extrapyramidal signs were present urinary amino acids were investigated by paper chromatography. Chlorpromazine was discontinued shortly after the appearance of extrapyramidal complications and immediately after the development of signs of liver damage.

RESULTS

Table 1 and 2 summarize the results of determinations of plasma copper, liver function, and extrapyramidal signs in the two groups of patients. In cases which did not have copper studies beyond the third or fifth week either the patients were discharged or the chlorpromazine was discontinued.

It is to be noted that the majority of the cases which were treated with chlorpromazine showed a gradual rise in plasma copper, in 12 of which it was definitely abnormal (beyond 160γ/100 cc.). Among these 12 cases, 5 manifested extrapyramidal signs (Cases 11, 19, 23, 24, and 25), and in 2 these signs were quite marked. In one case which evidenced liver damage (Case 21) there was a moderate rise in plasma copper. In no case was there a combination of plasma copper rise, liver damage (as judged by the tests used here), and extrapyramidal signs. No case manifested neurological signs without a rise in the plasma copper. Urinary amino acids were within normal limits in all cases showing neurological changes. There was no correlation between the dosage of chlorpromazine and the appearance or intensity of extrapyramidal complications.

In the control group there was no persistent pattern, no rise in plasma copper, or any neurological changes. It should be noted that extrapyramidal signs disappeared within a month after the cessation of chlorpromazine therapy in all cases.

TABLE 1.—*Cases Treated with Chlorpromazine*

	Plasma Copper, γ/100 Cc.*							
Case No.	Before	1st Week	3d Week	5th Week	7th Week	Amino Acids	Liver Damage	Extra-pyramidal Changes
1	117	145	174	...	...	.....	None	None
2	126	133	155	...	...	.....	None	None
3	109	126	168	157	...	.....	None	None
4	?	182	193	183	215	Normal	None	None
5	97	81	...	...	...	.....	None	None
6	125	107	161	...	...	.....	None	None
7	77	74	...	...	...	.....	None	None
8	112	137	130	...	...	.....	None	None
9	102	92	99	112	...	.....	None	None
10	144	121	154	...	...	.....	None	None
11	107	147	150	161	...	Normal	None	Slight
12	80	127	105	...	...	.....	None	None
13	99	129	120	...	...	.....	None	None
14	126	150	170	...	...	.....	None	None
15	116	125	170	...	...	.....	None	None
16	119	156	152	...	...	.....	None	None
17	77	83	134	112	...	.....	None	None
18	88	121	114	...	...	.....	None	None
19	141	163	147	...	...	Normal	None	Slight
20	120	120	...	...	...	.....	Present	None
21	?	183	153	...	...	Normal	Present	None
22	130	151	...	...	...	.....	Present	None
23	125	170	224	180	120	Normal	None	Marked
24	?	197	247	245	170	Normal	None	Marked
25	146	181	...	146	...	Normal	None	Moderate

* Normal levels for this laboratory 140-160 γ/100 cc.

COMMENT AND CONCLUSIONS

The data presented above demonstrate that chlorpromazine provokes an alteration of copper metabolism in the body. In those cases

which evidenced extrapyramidal changes the amount of plasma copper rose above the normal level, and fell within two weeks after the cessation of chlorpromazine. The normalization of plasma copper is more or less coincidental with the disappearance of neurological signs, which are always transitory.‡

The problem is to determine the nature of these alterations concomitant with chlorpromazine administration. Can these alterations be considered similar to Wilson's syndrome? It is well known that in Wilson's disease (hepatolenticular degeneration) the copper metabolism is disturbed, but the status of plasma copper is still controversial. Glazebrook,[11] Cumings,[4] and Mathews and associates [12] have reported that the plasma copper level in Wilson's disease is either normal or increased. Lahey [7] and Bearn [8] and their associates have found a decrease in the plasma copper level, and Cartwright and associates,[9] a decrease in the total plasma copper level, an increase in the direct-reacting fraction of plasma copper, and a decrease in the indirect-reacting (ceruloplasmin) fraction of plasma copper. Investigating 60 members of a family with Wilson's disease, one of us (H. A.[13]) found an increase in plasma copper and in ceruloplasmin in some cases (without manifest signs of Wilson's disease) and a decrease in other cases. Scheinberg and Gitlin [14] reported a decrease in ceruloplasmin "despite the fact that the copper level may be either higher or lower than normal." Because we did not measure the indirect-reacting fraction of plasma copper in the present series, we are not justified in concluding that there is an identity between the changes produced by chlorpromazine and by Wilson's disease. However, the similarity of the two conditions cannot be excluded because of the clinical picture of chlorpromazine complications (hepatic and lenticular), which is similar to that in Wilson's disease, and the fact that the copper metabolism was abnormal only in those cases which showed neurological signs.

TABLE 2.—*Cases Treated with Methods Other Than Chlorpromazine*

Case No.	Plasma Copper, γ/100 Cc. Before	1st Week	3d Week	5th Week	Extrapyramidal Changes
1	124	85	116	...	None
2	176	263	187	190	None
3	98	143	114	131	None
4	146	147	?	139	None
5	103	139	117	116	None
6	104	104	115	105	None
7	134	136	105	...	None
8	108	111	143	132	None
9	123	138	126	...	None
10	111	?	131	121	None
11	170	157	125	...	None
12	207	105	95	...	None
13	187	136	123	...	None
14	133	122	94	...	None
15	112	103	140	...	None
16	75	77	98	...	None
17	112	109	105	99	None
18	136	98	97	88	None
19	79	98	102	...	None
20	115	104	135	...	None
21	160	91	97	...	None
22	?	140	...	...	None
23	116	120	90	...	None
24	133	130	...	...	None
25	146	96	109	123	None

Further difficulties arise in regard to the role of liver damage in this disorder. In none of the cases reported here was there a combination of extrapyramidal signs, liver damage, and plasma copper rise. However, in one case (Case 21) there was an association of the liver damage and the plasma copper increase. It may be argued that if the drug had been continued in those cases which manifested liver changes, extrapyramidal signs might eventually have appeared. It may be further contended that the nonconcomitance of liver damage and extrapyramidal signs does not exclude hepatolenticular degeneration. On the contrary in many cases of Wilson's disease, particularly at the beginning, these two syndromes (hepatic and lenticular) may appear independently of one another. André and van Bogaert [15] have actually postulated two different genetic factors in Wilson's disease, one responsible for hepatic, and the other for basal ganglia, changes. Heuyer and associates [16] have added some confirmation for the thesis of genetic bimodality of Wilson's disease. It can be concluded that the copper metabolism is altered in chlorpromazine therapy. The data are

‡ References 1 and 2.

provocative in indicating some similarities between the complications of this therapy and Wilson's disease, but they are far from conclusive.

SUMMARY

The combination of extrapyramidal signs and liver damage in chlorpromazine-treated cases led to the study of copper metabolism.

The plasma copper level of 25 psychiatric cases was measured before and at the end of the first, third, and fifth weeks after the treatment with chlorpromazine. Urinary amino acids were investigated in cases which showed extrapyramidal signs. Liver function tests were performed in all cases. A control group consisted of 25 psychiatric cases which received other forms of treatment.

Twelve of the chlorpromazine-treated patients showed an abnormal increase in plasma copper, among whom five manifested extrapyramidal signs. In two these signs were quite marked; they consisted of cogwheel rigidity, tremor, loss of associated movements, mask-like facies, etc.

The theoretical aspects of the data are discussed in regard to any similarity to Wilson's disease.

REFERENCES

1. Azima, H., and Ogle, W.: Effects of Largactil in Mental Syndromes, Canad. M. A. J. **71**:116-121, 1954.

2. Lehmann, H. E., and Hanrahan, G. E.: Chlorpromazine: New Inhibitory Agent for Psychomotor Excitement and Manic States, A. M. A. Arch. Neurol. & Psychiat. **71**:227-237, 1954.

3. Stacey, C.; Azima, H.; Huestis, J. G.; Howlet, J. G., and Hoffman, M. M.: Jaundice Occurring During the Administration of Chlorpromazine, Canad. M. A. J. **73**:386-391, 1955.

4. Cumings, J. N.: The Copper and Iron Content of Brain and Liver in the Normal and in Hepatolenticular Degeneration, Brain **71**:410-415, 1948.

5. Denny-Brown, D., and Porter, H.: Effect of BAL on Hepatolenticular Degeneration (Wilson's Disease), New England J. Med. **245**:917-925, 1951.

6. Mandelbrote, B. M.; Stamer, M. W.; Thompson, R. H. S., and Thurston, M. N.: Studies in Copper Metabolism in Demyelinating Diseases of the Central Nervous System, Brain **71**:212-222, 1948.

7. Lahey, M. E.; Gubler, C. J.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: VII. Blood Copper in Pregnancy and Various Pathologic States, J. Clin. Invest. **32**:329-339, 1953.

8. Bearn, A. G., and Kunkel, H. G.: Abnormalities of Copper Metabolism in Wilson's Disease and Their Relationship to Aminoaciduria, J. Clin. Invest. **33**:400-409, 1954.

9. Cartwright, G. E.; Hodges, R. E.; Gubler, C. J.; Mahoney, J. P.; Daum, K.; Wintrobe, M. M., and Bean, W. B.: Studies on Copper Metabolism: XIII. Hepatolenticular Degeneration, J. Clin. Invest. **33**:1487-1501, 1954.

10. Gubler, C. J.; Lahey, M. E.; Cartwright, G. E., and Wintrobe, M. M.: Studies on Copper Metabolism: Method for Determination of Copper in Whole Blood, Red Cells and Plasma, J. Biol. Chem. **196**:209-220, 1952.

11. Glazebrook, A. J.: Wilson's Disease, Edinburgh M. J. **52**:83-87, 1945.

12. Matthews, W. B.; Milne, M. D., and Bell, M.: The Metabolic Disorder in Hepatolenticular Degeneration, Quart. J. Med. **21**:425-445, 1952.

13. Heuyer, G.; Baudoin, A.; Azima, H.; Faure, H.; Jérome, H., and Shmitt, H.: A propos de la Maladie de Wilson: Investigations généalogiques, cliniques, métaboliques, portant sur 60 membres d'une famille, Rev. neurol. **89**:165-181, 1953.

14. Scheinberg, I. H., and Gitlin, D.: Deficiency of Ceruloplasmine in Patients with Hepatolenticular Degeneration (Wilson's Disease), Science **116**:484-485, 1952.

15. André, M. U., and van Bogaert, L.: L'hérédité dans la dégénéréscence hépato-lenticulaire et le problème des rapports intrinsèques de la pseudo-sclérose de Westphal-Strümpell et de la maladie de Wilson: La situation nosologique de l'"abdominal-Wilson" de Kehrer au sein de la D. H. L., Encéphale **39**:1-54, 1950.

Functional State of Basal Ganglia in Extrapyramidal and Convulsive Disorders

An Electrographic Study

E. A. SPIEGEL, M.D.
H. T. WYCIS, M.D.
H. W. BAIRD III, M.D.
and
E. G. SZEKELY, V.M.D., Philadelphia

Electrography of the striatum and pallidum was guided by the consideration that it may provide an answer as to the participation of these structures in the mechanism of extrapyramidal and convulsive disorders. In an individual case such recordings may help to decide whether elimination or reduction of the activity, particularly of parts of the pallidum, may serve a useful purpose; postoperatively, such recordings may give an indication as to whether the procedure employed was able to change the functional state of the pallidum.

MATERIAL AND METHODS

Since the recordings and operative procedures had to be performed in several stages, a new type of stereoencephalotome (Model V) was constructed. It permits one to apply the apparatus repeatedly in exactly the same position. The apparatus is fixed to the skull by means of four screws that carry small steel balls, to which the feet of the stereoencephalotome may be attached in any position. The length of these feet can be varied; on their upper end they are connected to the basal ring by a universal joint, so that the base can be easily placed in a position parallel to the plane determined by the Frankfurt horizontal lines. In the basal ring a rectangular frame can be rotated and can be moved forward or backward. The electrode holder can be moved on the frame to the left or to the right and can be rotated in a frontal or a sagittal direction. A detailed description of this apparatus will be published elsewhere.

The electrodes are insulated silver wires, 0.0055 in. in diameter; their bare ends are changed into small balls by heating. Two to three electrodes are cemented to each other so that the balls are 2-3 mm., apart. These electrodes are held in a polyethylene tube (inner diameter 0.023 in., outer diameter 0.038 in.) so that only their balls are protruding. The extracranial end of the tube may be connected to a syringe so that an anesthetic solution may be injected into the ganglion under study after the recording. Thus, preceding the definitive destruction of a part of a ganglion by electrolysis or electrocoagulation, its functional state can be ascertained by electrography and the advisability of such an operation can be tested also by transitory elimination of the ganglion by procaine (Novocaine).

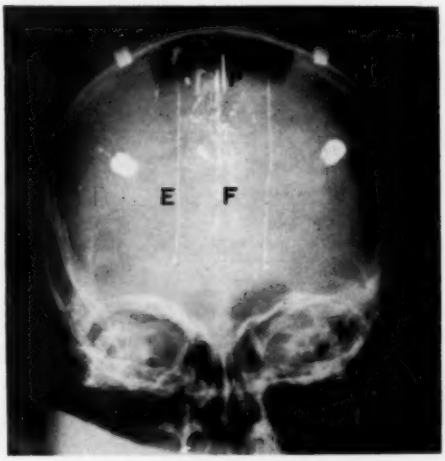


Fig. 1.—Anteroposterior view. *E* indicates depth electrodes in pallidum; *F*, iophendylate (Pantopaque) droplets alongside falx; *P*, pins in skull indicating median plane (intersection with superior longitudinal sinus); *S*, screws.

Received for publication Oct. 28, 1955.

Aided by Grant No. B-470 of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Department of Health, Education, and Welfare.

From the Departments of Experimental Neurology, Neurosurgery, and Pediatrics, Temple University School of Medicine and Hospital and St. Christopher's Hospital for Children.

In order to determine the coordinates for electrode placement, the foramen of Monro is visualized by pneumoencephalography and the position of the falx outlined by subdural injection of iophendylate (Pantopaque) through a fine polyethylene tube introduced between the falx and the medial wall of the hemisphere. This permits one to localize the electrodes in relation to the median sagittal plane also after the air in the ventricles and the subarachnoid space has been absorbed (Fig. 1).

Our material comprises three cases of athetosis (two children with cerebral palsy, one adult with posthemiplegic athetosis), one patient with senile chorea associated with torsion spasms of the neck muscles, five patients with resting tremor (two with paralysis agitans, two with postencephalitic Parkinsonism, one with head tremor), and four patients with generalized tonic-clonic convulsions (of undetermined origin in three and accompanying tuberous sclerosis in one).

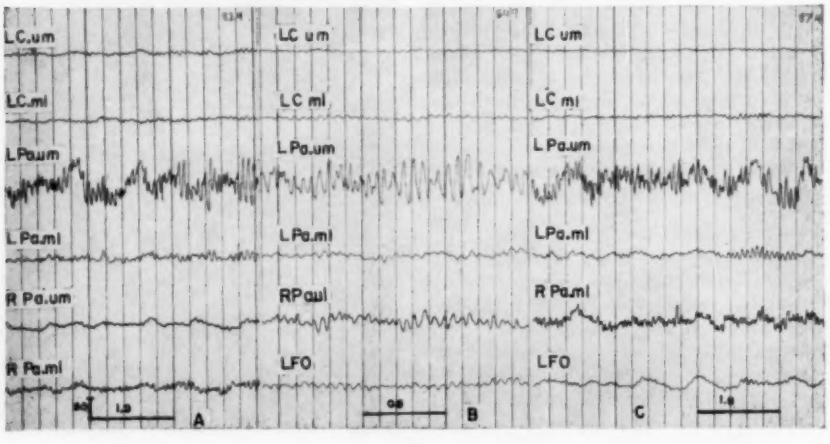
RESULTS

In cerebral palsy associated with athetosis definite rhythmic discharges of the striopallidum were found to be preserved. The lowest frequency observed was 5-6/sec.; it was recorded from the pallidum of a 15-year-old athetotic patient; the highest frequency (21-29/sec.) was led off from the striatum and pallidum, as well as from the scalp, of a 12-year-old cerebral palsy patient with athetosis. According to our experiences in animals (cats), the frequencies in the striopallidum do not differ significantly from those of the cortex. Hayne and associates [5] observed in adult patients without extrapyramidal disorders (psychotic patients and patients with carcinoma of internal organs) frequencies between 6 and 19 per second. Considering that frequencies of 5/sec. can be found in the scalp EEG up to the age of 19 (Henry [7]), one would hardly be justified in regarding the frequencies led off from the striopallidum in the athetotic children as pathologic. However, under the influence of drugs, asymmetries of pallidal records, particularly high-amplitude discharges from this ganglion could be observed, e. g., on the patient's awakening from barbiturate anesthesia or after injection of reserpine (Serpasil; Figs. 2 and 3). Figure 3 shows during the action of this drug, when the patient fell asleep, a slowing of the waves in the caudate nucleus and the appearance of sharp, irregular waves in the pallidum, while the changes in the fronto-occipital scalp leads (slight increase in the amplitude and irregularity of the record) were less pronounced. In single instances the appearance of slow waves in the caudate nucleus was

Fig. 2.—Cerebral palsy with athetosis; tracings taken on awakening from barbiturate anesthesia.

Depth electrodes in left caudate nucleus (*LC*) and left and right pallida (*L Pa*; *R Pa*), three electrodes (*u*, upper; *m*, middle; *l*, lower) in each ganglion. *LFO*, left fronto-occipital scalp electrodes.

Time: 1 second in *A* and *C*; 0.5 second in *B*. Standardization: 50μv.



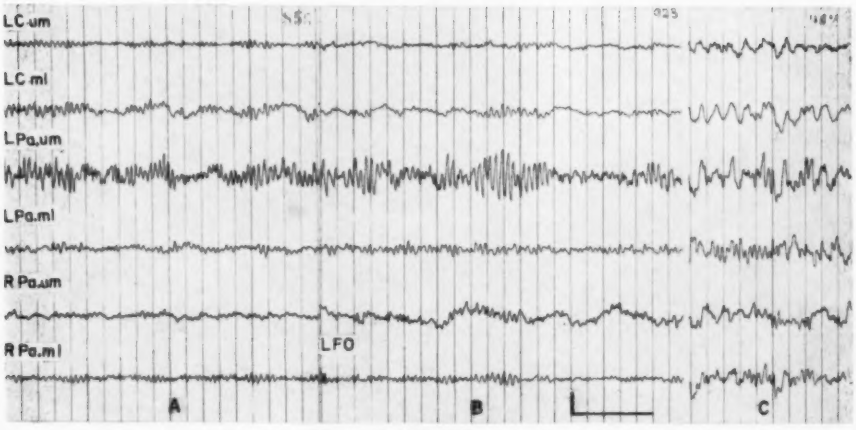


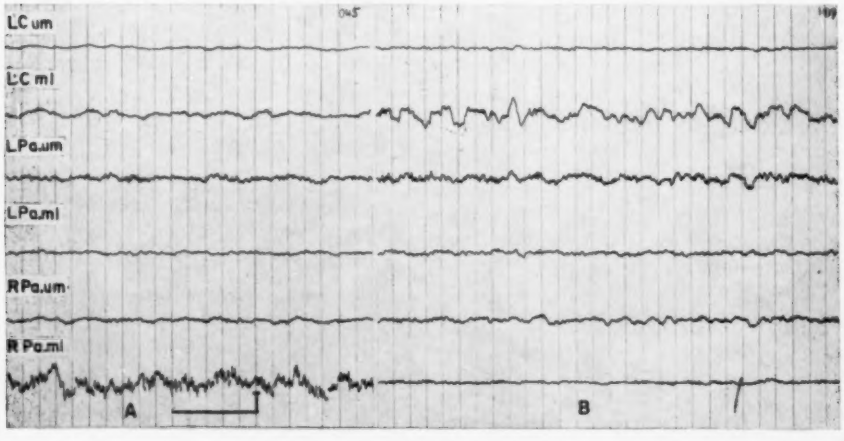
Fig. 3.—Same patient as in Figure 2. Tracings taken two and a half hours after intramuscular injection of 2 cc. of reserpine (Serpasil).
A and *B*: patient awake; *C*: patient asleep.
Time: 1 second. Standardization: 50μv.

noted, e. g., after administration of bulbocapnine (Fig. 4). However, one must bear in mind that animal experiments (Szekely and Spiegel[14]) reveal a certain susceptibility of the basal ganglia to the action of this drug.

Meprobamate (Miltown; Equanil; 2-methyl-2-*n*-propyl-1, 3-propanediol dicarbamate), a recently developed derivative of mephenesin, produced a pronounced slowing and increase of amplitude in the caudate nucleus in particular, while the effect on the scalp EEG was less striking (Fig. 5). These changes in the records from the basal ganglia were much more marked than in those of cortical and thalamic activity of cats published by Hendley, Lynes, and Berger.[6]

In a case of chorea senilis with dystonic features (torsion spasms of the neck muscles), records (Fig. 6*A* to *G*) obtained during phases when the head movements were at a minimum showed slow (5-7/sec.) waves appearing irregularly in the striatum (putamen) and pallidum, sometimes simultaneously in the two ganglia (Fig. 6*E*), and

Fig. 4.—Same patient as in Figure 2. Effect of subcutaneous injection of 5 mg/kg. of bulbocapnine HCl. *A*, before; *B*, after injection.



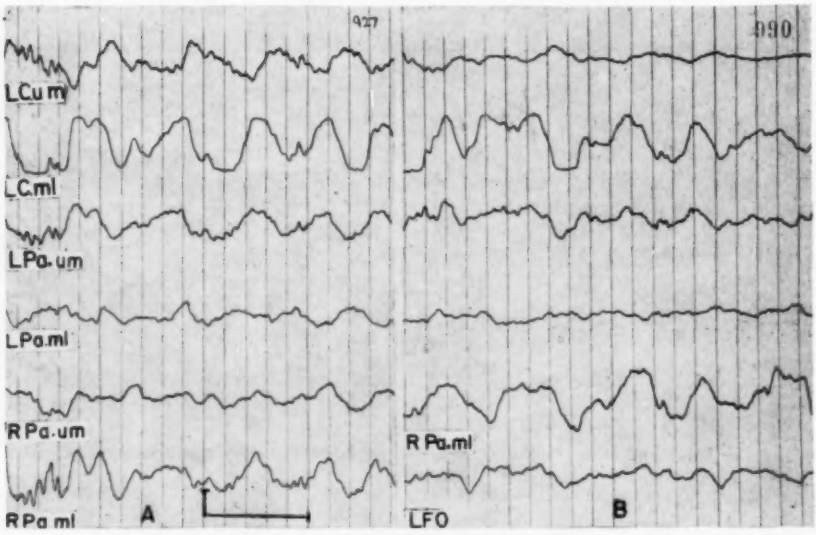


Fig. 5.—Same patient as in Figure 2. Effect of meprobamate (Miltown), 33 mg. per kilogram.

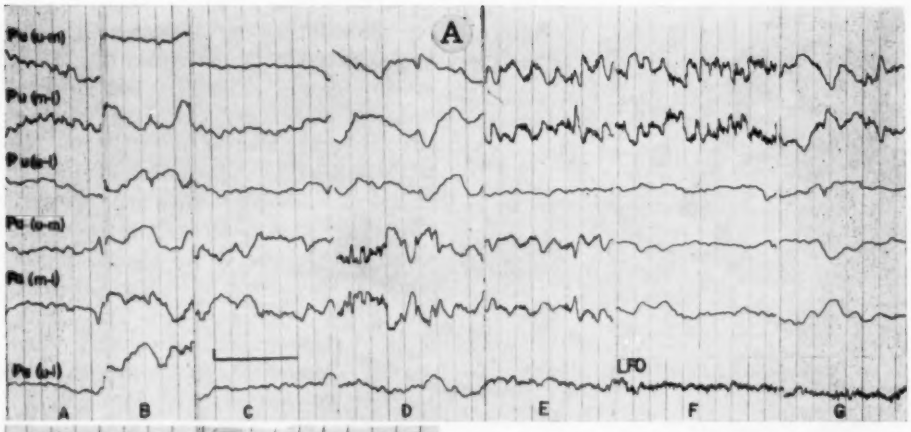
sometimes in the putamen or pallidum only; they were accompanied by fast activity in the scalp leads. With the patient under general anesthesia regular 6/sec. waves were noted in the striopallidum, as well as the scalp EEG (Fig. 6*H*, *I*), together with the disappearance of the involuntary movements.

In a hemiplegic woman with athetosis of the left hemiplegic side, particularly of the left hand, developing after a cerebrovascular accident, the electrical discharges of the right caudate nucleus were definitely reduced as compared with those on the left side, which showed a 5-6/sec. rhythm (Fig. 7). This pattern seems to be the electrographic counterpart of pathoanatomic observations of focal lesions in the caudate nucleus contralateral to hemichorea or hemiathetosis (for references on these histopathologic changes see Spatz [11]).

In agreement with our previous observation (Spiegel and Wycis [12]), rhythmic pallidal discharges that apparently did not deviate significantly from the normal were recorded in paralysis agitans and Parkinsonism and in a case of vertical head tremor associated with jerking of the head to the left side.

The effect of three types of operative procedures upon the pallidal activity could be studied: ligature of the anterior choroidal artery (Cooper [2]), injection of tetracaine (Pontocaine) HCl, and electrolysis. In a patient with postencephalitic Parkinsonism in whom a unilateral ligature of the anterior choroidal artery had been performed elsewhere, the pallidogram on the side of the operation showed that this procedure apparently had not significantly altered the electrical discharges of this ganglion (Fig. 8). This observation is not surprising in view of the known variability in the extent of the area supplied by the anterior choroidal artery; it merely illustrates that ligation of this artery does not regularly affect the functional activity of the globus pallidus. Following tetracaine HCl infiltration of the pallidum or electrolysis of this ganglion with an anodic current of 10 ma., its electrogram became quite flat or did not exceed the noise level of the recording system (Fig. 9).

Simultaneous records of the scalp EEG and of the electrogram of the basal ganglia in cases of generalized tonic-clonic convulsions showed various relationships between the seizure discharges recorded from the scalp



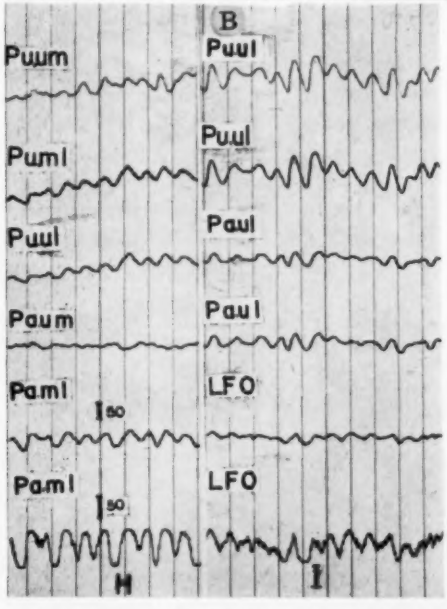


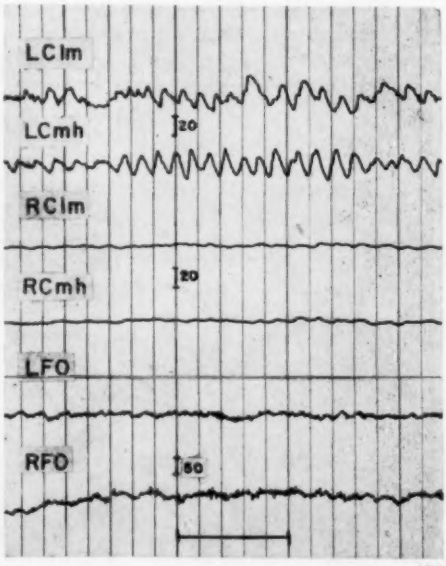
Fig. 6.—Senile chorea with dystonia. *A-G*, patient in waking state; *H*, *I*, patient asleep.

Depth electrodes in the pallidum (*Pa*) and putamen (*Pu*); upper (*u*), middle (*m*), and lower (*l*) electrode in each ganglion. *LFO*, left fronto-occipital electrodes.

Time: 1 second. Standardization: 50μv.

and those from the depth electrodes. Sometimes the bursts appeared simultaneously in the cortex and in the basal ganglia, or they followed in the striopallidum the cortical discharges; this is in agreement with animal experiments (Walker and associates,[3] Hayashi [4]). Of particular interest are the observations of seizure discharges that apparently originated in the depth of the brain. In an epileptic patient in whom the scalp EEG showed only rather indefinite seizure discharges, very distinct bursts could be noted bilaterally in the pallidogram, similar to observations of R. Meyers [9] in thalamic and striatal recordings (Fig. 10). Whether the discharges originate in the basal ganglia or

Fig. 7.—Posthemiplegic athetosis affecting the left hand. Electrodes in the left and right caudate nuclei (*LC*, *RC*); (*l*, *m*, and *h*) lowest, middle, and highest electrodes. *LFO* and *RFO*, left and right fronto-occipital scalp electrodes.



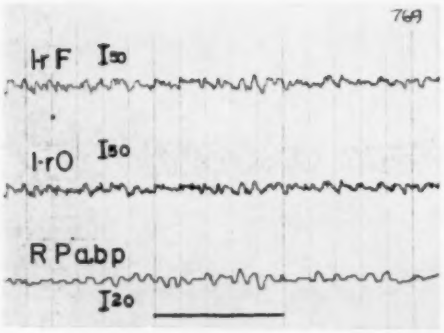


Fig. 8.—Postencephalitic Parkinsonism; tracings taken following ligation of the right anterior choroid artery. *R Pa. bp*, bioplar record from right pallidum; *l-r F* and *l-r O*, bipolar records from the left and right frontal and left and right occipital leads, respectively.

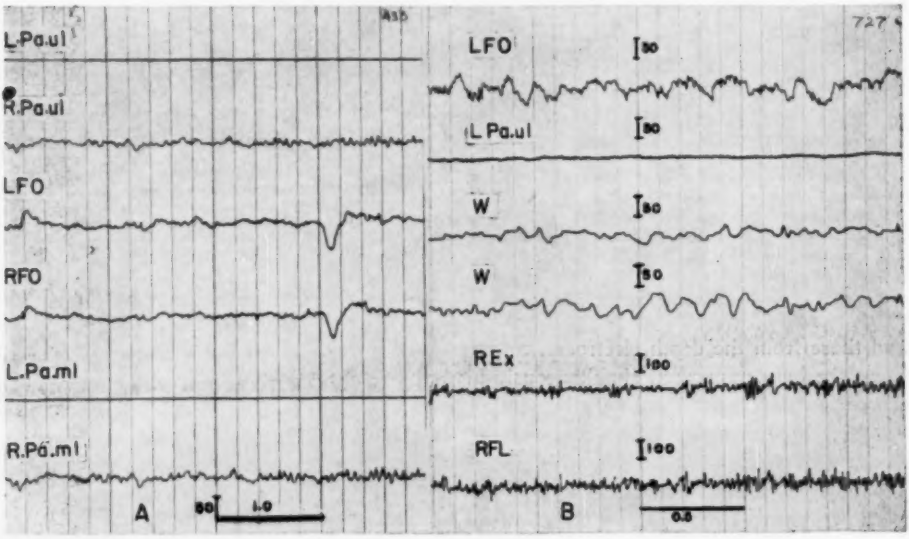
in other parts of the subcortex cannot, of course, always be ascertained in patients, since only a rather limited number of depth electrodes can be inserted. Occasionally, however, the epileptogenic focus can be located, as in the case of a boy with generalized convulsions that were a manifestation of tuberous sclerosis; the pneumoencephalogram revealed a nodule in the region of the right caudate nucleus (Fig. 12). The electropallidogram taken on the side of this nodule simultaneously with scalp EEG's and electrothalamograms showed that the pallidal discharges had the maximum amplitude (Fig. 11). This encouraged us to produce electrolytic lesions of the nodule and the adjoining pallidum, after which procedures the epileptic seizures ceased. The duration of the postoperative observation (eight months) is too short on which to base the assertion that this effect is permanent.

COMMENT

Our knowledge of the physiopathology of the diseases of the so-called extrapyramidal system and of the functions of the basal ganglia in man is based on histopathologic studies. Unfortunately, here one deals mostly with diffuse diseases, and experiences with circumscribed, isolated lesions of single parts of this system are rather rare. As a result,

Fig. 9.—*A*, athetosis, after injection of 1% tetracaine HCl, 0.5 cc., into the left pallidum (*L Pa*)A. *R Pa*, right pallidum; *u*, *m*, *l*, upper middle, and lower depth electrodes; *LFO* and *RFO*, left and right fronto-occipital scalp electrodes respectively.

B, paralysis agitans; electrolysis of the left pallidum (*L Pa*); *u*, upper, and *l*, lower electrode. *LFO* left fronto-occipital scalp electrodes; *REx* and *RFL*, electromyograms of extensor and flexor muscles of right forearm; *W*, white matter.



conclusions based upon such histopathologic studies are frequently contradictory. For instance, such an experienced pathologist as Jakob [8] concluded from his material that in athetosis of adults the pallidum is always affected, while cases are on record in which this ganglion was found to be intact (Richter,[10] Steck;[18] see also Carpenter [1]). Furthermore, the histopathologic studies reveal only terminal stages, in which the athetotic movements are often masked or replaced by the development of contractures, so that

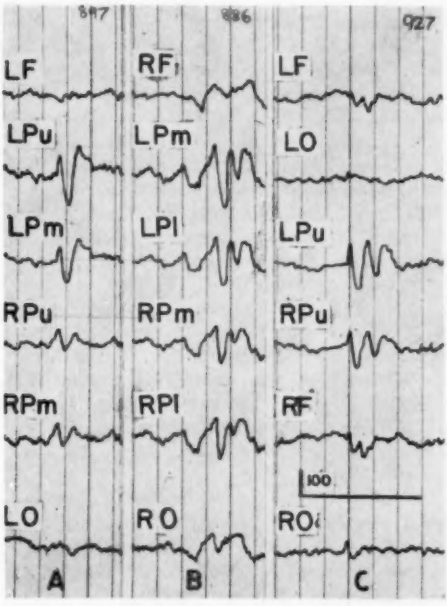


Fig. 10.—Epileptic with generalized tonic-clonic convulsions. Records taken with depth electrodes in the left and right pallida (*LP, RP*) in a seizure-free interval reveal high-amplitude discharges, while scalp electrodes in the left and right frontal (*LF, RF*) and occipital (*LO, RO*) regions show no, or rather indefinite, seizure discharges; *u, m,* and *l,* upper, middle, and lower pallidal electrodes.
Time: 1 second. Standardization 100μv.

a correlation between the functional state of the basal ganglia at the time of the athetotic movements and the morphologic changes in the various ganglia is hardly possible. The development of a technique permitting one to insert electrodes stereotactically, and thus to study the electrical activity of various ganglia and to eliminate parts of them, offers one the possibility of supplementing the re-

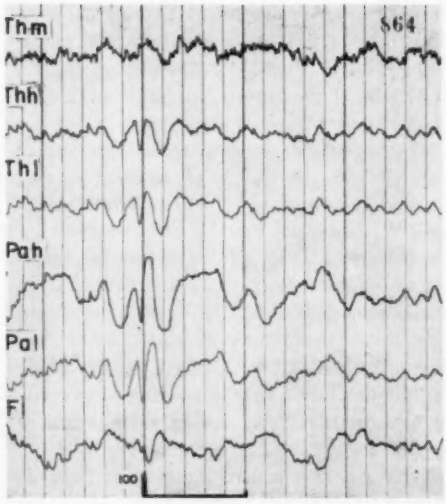
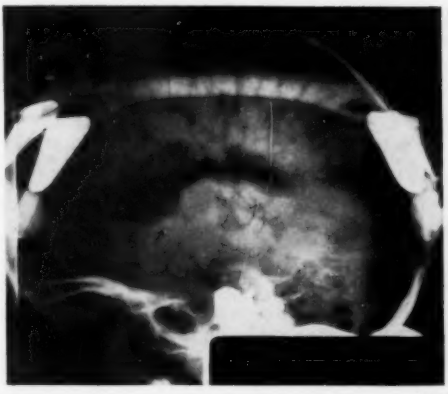


Fig. 11.—Tuberous sclerosis with generalized tonic-clonic convulsions. Nodule in the right caudate nucleus revealed by air studies (Fig. 12). Depth electrodes on this side show seizure discharges with higher amplitude in the pallidum (*Pa*) than in the thalamus (*Th*); *h, m,* and *l,* highest, middle, and lowest electrode; *F,* frontal scalp electrode.

sults of histopathologic studies, and perhaps of clarifying some of the issues. Our preliminary studies in cases of athetosis suggest not only that the activity of the pallidum may be preserved but also that there may be an increased reactivity of its cells, e. g., to the action of some toxins. However, it should be emphasized that it would be premature at present to develop a general theory

Fig. 12.—Tuberous sclerosis. Nodule indicated by arrow.



of hyperkinetic states and that in each individual case of hyperkinesis a careful analysis, including depth electroencephalography of the basal ganglia, is advisable before an operative procedure is considered.

A comparison of scalp recordings and of electrography of the basal ganglia in convulsive disorders vividly demonstrates that scalp EEG's alone provide only a rather incomplete picture of seizure discharges originating in various parts of the brain. It is, of course, impossible to carry out depth electroencephalography routinely in convulsive disorders. However, in cases in which additional studies, e. g., air encephalography, suggest the possibility of a subcortical epileptogenic focus the electrographic study of the suspected subcortical region may be rewarding not only from a theoretical but also from a practical point of view, as shown by the above-described case of tuberous sclerosis.

SUMMARY

By means of stereotactically introduced depth electrodes, bipolar electrograms of the striatum and pallidum were recorded, together with scalp EEG's in cases of athetosis, chorea senilis, paralysis agitans, and generalized tonic-clonic convulsions.

While rhythmic discharges at frequencies that apparently lie within the normal range of variability may be obtained from the striopallidum in cases of athetosis, an increased amplitude of pallidal discharges may appear under the influence of toxins. In a case of posthemiplegic hemiathetosis the discharges from the opposite caudate nucleus were significantly lower than those from the corresponding homolateral ganglion. Pathologic changes of the pallidal discharges in paralysis agitans or Parkinsonism could not be found.

Electrography of the striopallidum in extrapyramidal disorders may help one to ascertain the functional state of these ganglia if one is considering operative intervention, such as pallido-ansotomy. It may also be useful in determining the changes induced by an operative procedure on the basal ganglia.

In some instances of convulsive disorders the electrograms of the striopallidum may reveal much more definite seizure discharges than do the scalp EEG's. An observation in a case of tuberous sclerosis indicates that there is a type of epileptiform seizure that originates in the striopallidum and that this type is amenable to treatment by destruction of foci located in this area.

REFERENCES

1. Carpenter, M. B.: Athetosis and the Basal Ganglia, Arch. Neurol. & Psychiat. **63**:875-901, 1950.

2. Cooper, I. S.: Ligation of the Anterior Choroidal Artery for Involuntary Movements—Parkinsonism, Psychiat. Quart. **27**:317-319, 1953.

3. Faeth, W. H.; Walker, A. E., and Andy, O. J.: Propagation of Cortical and Subcortical Epileptic Discharge, Epilepsia, Series 3, pp. 37-48, 1954.

4. Hayashi, T.: A Physiologic Study of Epileptic Seizures Following Cortical Stimulation in Animals, Japan. J. Physiol. **3**:46-64, 1952.

5. Hayne, R.; Meyers, R., and Knott, J. R.: Characteristics of the Electrical Activity of the Human Corpus Striatum and Neighboring Structures, J. Neurophysiol. **12**:185-195, 1949.

6. Hendley, C. D.; Lynes, T. E., and Berger, F. M.: Effect of 2-Methyl, 2-*n*-Propyl-1, 3-Propanediol Dicarbamate (Miltown) on Central Nervous System, Proc. Soc. Exper. Biol. & Med. **87**: 608-610, 1954.

7. Henry, C. E.: Electroencephalograms of Normal Children, Washington, D. C., National Research Council, 1944.

8. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Springer-Verlag, 1923.

9. Meyers, R.: Surgical Treatment of Focal Epilepsy, Epilepsia, Series 3, pp. 9-36, 1954.

10. Richter, H.: Beiträge zur Klinik und pathologischen Anatomie der extrapyramidalen Bewegungstörungen, Arch. Psychiat. **67**:226-294, 1923.

11. Spatz, H.: Physiologie und Pathologie der Stammganglien, in Bethe, H.; Handbuch der normalen und pathologischen Physiologie, Berlin, Springer-Verlag, 1927, Vol. 10, pp. 318-417, particularly p. 364.

12. Spiegel, E. A., and Wycis, H. T.: Ansotomy in Paralysis Agitans, A. M. A. Arch. Neurol. & Psychiat. **71**:598-614, 1954.

13. Steck, H.: Zur pathologischen Anatomie der echten posthemiplegischen Athetose, Schweiz. Arch. Neurol. u. Psychiat. **8**:75-85, 1921.

14. Szekely, E. G., and Spiegel, E. A.: The Effect of Bulbocapnine upon the Spontaneous Electric Activity of the Brain and Its Reactivity to Afferent Stimuli, Electroencephalog. & Clin. Neurophysiol. **6**:213-219, 1954.

Fungus Infections of the Central Nervous System

Experience in Treatment of Cryptococcosis with Cycloheximide (Actidione)

LOUIS D. BOSHES, M.D.
IRVING C. SHERMAN, M.D.
CHARLES J. HESSER, M.D.
ALBERT MILZER, M.D.
and
HELEN MacLEAN, B.A., Chicago

Fungus infections in man until recently were not considered serious involvements, but this premise is no longer valid. Accurate vital statistics are not available on the fatalities from fungus infections, since this cause of death is rarely recorded. In 1951 the U. S. Vital Statistics recorded 338 persons who succumbed to systemic fungus diseases. Of those who do not die, many become disabled with the residua and the sequelae. Nickerson [1] has postulated that "fungus infections are probably the most widely distributed and most numerous types of infections."

In certain areas in the United States, specific exogenous fungus diseases may be considered endemic. These include coccidioidomycosis, in the Southwest, ranging from western Texas to southern California, and histoplasmosis, in the lower two-thirds of the Mississippi River Valley and in southeastern states. Other fungus infections are uniformly distributed. Some of endogenous origin are actinomycosis, cryptococcosis, and moniliasis; others of exogenous origin include aspergillosis, nocardiosis, and penicilliosis.

Recorded for publication Dec. 20, 1955.

From the Division of Neuropsychiatry and Departments of Medicine and Microbiology, Michael Reese Hospital, and the Department of Neurology and Psychiatry, Northwestern University Medical School.

Smith [2] has observed that fungus illnesses are more frequent than diseases such as hemophilia, primary polycythemia, and even Addison's disease. Public health officials, microbiologists, pathologists, and even veterinarians are more aware of the growing numbers of cases heretofore not seen, or even suspected. Recently Zimmerman,[3] reporting in a Symposium on Diseases Caused by Fungi, noted that three factors were largely responsible for the mounting interest in medical mycology. These are (1) improved techniques for the diagnosis of fungus diseases by culture, animal inoculation, histopathology, serology, and skin testing; (2) an awareness that several mycoses once believed to be rare and invariably fatal actually are common subclinical infections that only occasionally lead to death, and (3) increasing frequency of fungus infections as important, and sometimes lethal, complications of other, primary diseases.

As long ago as 1861 Zenker [4] reported the case of a man who died of a fungus infection of the central nervous system which, in all likelihood, would now be diagnosed as cryptococcosis. Such cases have recently been reported with increasing frequency. Sahs [5] reviewed the work of observers who studied the fungi that invade the central nervous system. He noted that Blastomyces dermatitidis is known to produce a granulomatous meningitis with miliary abscess formation; actinomyces, a meningitis and/or brain abscess; and Coccidioides immitis, a granulomatous meningitis about the brain and cord with little involvement of the parenchyma. In this group perhaps the most widely known agent is Cryptococcus neo-

formans (torulosis). Freeman,[6] describing the pathologic process, likened it to a meningeal response, such as that seen in tuberculosis, with perivascular lesions extending from the subarachnoid space into the cortex. Secondary embolic lesions may produce honeycomb-like cysts in the basal ganglia or in the cortex. In addition to causing meningitis or meningoencephalitis, torulosis may present the features of a space-occupying lesion in the brain or spinal cord (Alajouanine, Houdart, and Drouhet [7]).

Other rare cases, with the following etiologies, have also been described: A low-grade meningitis may be produced by Candida albicans (moniliasis). Hyslop, Neal, Kraus, and Hillman [8] have reported a case of a gelatinous basilar meningitis caused by Sporotrichum schenckii. These observers, however, failed to isolate the invading organism by culture. Wolf and colleagues [9] reported a case of maduromycotic meningitis following spinal anesthesia. Allescheria boydii was isolated in repeated cultures. Pathologically, granulomatous meningitis was noted. Cerebral mucormycosis has been observed to produce localized cerebritis without evidence of suppuration. A tendency to invade the walls of blood vessels and occlude the lumina is characteristic (Kurrein [10]). Aspergillosis may cause meningitis, as well as isolated or multiple brain abscesses.

Our interest in this subject was aroused when in the period of 10 months at the Michael Reese Hospital, Chicago, we encountered one case of cerebral aspergillosis (with associated moniliasis) and three cases of cerebral cryptococcosis. During this period we also had access to the clinical and pathologic material of a case of coccidioidomycosis seen at the Veterans Administration Research Hospital in the same city. A thorough search of the records at Michael Reese Hospital revealed that between 1935 and 1954 only four cases of fungus infections of the central nervous system were recognized. Of these, two were of cryptococcosis (1934, 1941); one, of actinomycotic meningitis (1939), and one, of actinomycotic brain abscess (1949). These observations are similar to the experiences at Mount Sinai Hospital in New York, where, in 1951, Globus, Gang, and Berman [11] described the only two cases of Torula meningoencephalitis that had appeared there in the previous 25 years. No specific mention was made of other fungus types. In a footnote to their article, the authors noted that Carton [12] had, to date, reports of only 225 cases of human cryptococcosis, almost all of which involved the central nervous system.

The occurrence of five cases of fungus infections involving the central nervous system in a relatively short period of time was considered worthy of report. At the same time, it was felt opportune to test some of the newer therapies because until now treatment has been only symptomatic and supportive. We utilized routinely a relatively recent variation of staining technique known as the periodic-acid-Schiff reagent (P. A. S.), or the Hotchkiss-McManus technique (Kligman and Mescon [13]).

CRYPTOCOCCOSIS

CASE 1.— Diagnosis: Cryptococcosis (courtesy of Dr. Edwin R. Levine).

A 17-year-old white girl was admitted to Michael Reese Hospital, Chicago, on March 29, 1954, because of headache, nausea, and vomiting.

History.—The patient became ill at the age of 13 (December, 1950), when biopsy of an enlarged lymph node led to the diagnosis of Hodgkin's disease. She was admitted to Michael Reese Hospital for the first time on Feb. 3, 1951, for swelling in the left neck region, weakness, and a dull ache in the midback area. Starting in February, 1951, she received several courses of radiation to the anterior and posterior abdomen, right and left cervical lymph nodes, and right and left axillae. During February, 1954, she received a final course of nine x-ray treatments for enlarged cervical lymph nodes. Her final admission to Michael Reese Hospital was on March 29, 1954, when she complained of frontal headaches, accompanied by nausea and vomiting, which had been present for the preceding week.

Physical and Laboratory Findings.—On admission to the hospital, the patient was extremely pale and dehydrated. She complained of severe frontal headaches. She had bilateral enlargement of the cervical and supraclavicular lymph nodes. A large left inguinal node was also present, and all were fixed and nontender. The liver was palpable 4 fingerbreadths below the right costal margin, and

the spleen was palpable 3 fingerbreadths below the left costal margin. Within a few days the patient developed positive Brudzinski and Kernig signs bilaterally. The abdominal reflexes were absent. Tendon reflexes were hyperactive, with a prolonged ankle clonus and increased plantar reflexes bilaterally. An Oppenheim reflex and a positive Hoffmann sign were present on the right.

Hemoglobin 9.2 gm/100 cc.; RBC 3,100,000 per cubic millimeter, and WBC 9400 per cubic millimeter (71% polymorphonuclear leucocytes, 10% nonsegmented polymorphonuclear leucocytes, 14% lymphocytes, and 5% monocytes). Otherwise the blood and urine showed no abnormality. Chest x-rays revealed right mediastinal and hilar adenopathy and probably left hilar adenopathy. There was extensive pulmonary consolidation in the right middle lobe and in the left lower lobe. The costophrenic angles were sharply defined and free of fluid. The pulmonary consolidation probably represented Hodgkin's infiltration. X-rays of the skull and upper gastrointestinal tract were normal.

Hospital Course.—On April 2, 1954, the spinal fluid examination revealed a pressure of 350 mm. of water. The fluid was clear and contained 4 fresh RBC per cubic centimeter, 50 WBC per cubic centimeter (15 lymphocytes, 29 polymorphonuclear leucocytes, and 6 large mononuclear cells), and a 1+ Pandy reaction. The glucose was 44 mg/100 cc.; protein, 120 mg/100 cc.; chlorides, 667 mg/100 cc. Two days later the culture was reported as showing budding yeast cells morphologically resembling C. neoformans. This report was later confirmed by mouse inoculation. An EEG, on April 16, was interpreted as suggestive of subcortical (diencephalic) or diffuse cerebral pathology.

Numerous spinal punctures were done, and the pressure was found to be as high as 540 mm. of water. Yeast cells were cultured from each of the fluids after 48 hours' incubation. Organisms were occasionally seen in direct smear. Skin tests with PPD, histoplasmin, blastomycin, and coccidioidin and blood culture were all negative.

The patient ran a febrile course, with the temperature reaching 103 F at times. Therapy constituted of penicillin in intramuscular doses of 1,000,000 units daily, starting on the eighth hospital day. Three days later sodium sulfadiazine was added. On April 13 (17th hospital day) cycloheximide was started and given intravenously. This medication was continued throughout the remainder of her illness. For 15 days she received an average of approximately 60 mg. daily, and for the rest of her illness about 150 mg. daily, for a total of 6590 mg. After the 32d day, she received cycloheximide intrathecally in doses of 10 mg., and later 20 mg., first weekly, then twice a week, and later daily, for a total of 160 mg. On the 32d hospital day, an autogenous vaccine of the cryptococci was prepared and therapy started in the usual increasing strengths intradermally. On April 23, the 27th hospital day, a lymph node was excised from the left axilla and portions sent to the microbiology and pathology department. Five days later, the pathology report was "Hodgkin's sarcoma with no inflammatory reaction." On the same day, a positive culture for C. neoformans was obtained from the other half of the lymph node. At this time bilateral papilledema was first noted.

She showed no significant response to any of the therapeutic regimen, including potassium iodide and repeated spinal punctures. She developed motor aphasia, slight nuchal rigidity, and, finally, a generalized flaccid state. Her condition deteriorated gradually. She became dyspneic and cyanotic, and respirations ceased on June 10, ten weeks after admission.

Autopsy Findings.—Cultures taken at autopsy from the cisternal spinal fluid, subarachnoid space of the cerebral convexity, lung lesions, mediastinal and periportal lymph nodes, kidney, and spleen were positive for C. neoformans. The heart blood culture were negative for cryptococci.

Granulomata seen in the visceral pleura in the vicinity of the small bronchi lymph nodes, the heart, and the spleen revealed multinucleated giant cells typical of the Reed-Sternberg type.

The external surface of the brain was grossly normal except for a dubious thickening of the meninges in one spot near the interpeduncular area on the basis pontis. The cerebellum and brain stem were normal. In the region of the head of the caudate nucleus and part of the lenticular nucleus on both sides was a honeycomb-like area of pathology which was filled with a colloid-like material (Fig. 1). This pathology did not involve the thalamus on either side. Grossly, it did not invade the white matter. The spinal cord was essentially normal except for a thick plastic exudate over the cauda equina. Microscopic examination of the brain stained with hematoxylin and eosin and P. A. S. revealed C. neoformans in the meninges, particularly in the subarachnoid space, as well as in the brain parenchyma in the area of the honeycomb lesion, already described (Fig. 2). These were small round bodies with an occasional single budding, stained intensely violet by the P. A. S. stain (Fig. 3). The organisms were also clustered in the honeycomb lesion, surrounded by very little cellular infiltration and containing no cells (Fig. 4). The organisms were found in and around the capillaries. Sections of the plastic exudate found grossly at the region of the cauda equina showed necrotic debris, without any recognizable organisms, and this suggested a nonspecific reaction to intrathecal medication. Elsewhere, sections of the cord were normal, and there was no invasion of the meninges of the cord by cryptococci.

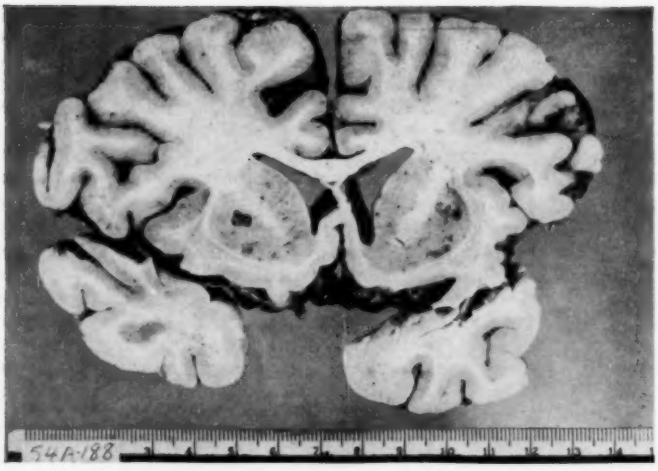


Fig. 1 (Case 1).—Gross brain section. Honeycomb areas of histolysis in basal ganglia bilaterally, containing colloid material.

Summary.—This patient had Hodgkin's disease for three years prior to the development of meningoencephalitis. C. neoformans was identified in the spinal fluid. Intensive cycloheximide therapy did not appear to influence the course of the illness, and the patient died about 10 weeks after admission. Pathologically, there was evidence of Hodgkin's disease in the lymph nodes, spleen, lungs, and heart, and of cryptococcosis involving the meninges, brain, and, probably, lungs.

CASE 2.—Diagnosis: Cryptococcosis (courtesy of Dr. B. Rubenstein).

A 36-year-old white man was admitted to Michael Reese Hospital on April 22, 1954, because of headache and diplopia, of several weeks' duration.

History.—The patient was a carpenter contractor, who had lived in Illinois all his life. He was well until 1950, when he developed a migratory polyarthralgia with heat, redness, swelling, and deformities of the joints. Early, he was treated with acetylsalicylic acid and physical therapy, but in 1952 he was started on corticotropin of unknown amounts and then put on cortisone in increasing doses to a maximum of 100 mg. daily. This treatment was continued for at least two years. In the spring of 1953 he suffered bouts of transient edema and hyperpyrexia, along with headache and diplopia. In his local hospital, a diagnosis of lymphocytic choriomeningitis was made on the basis of lymphocytes

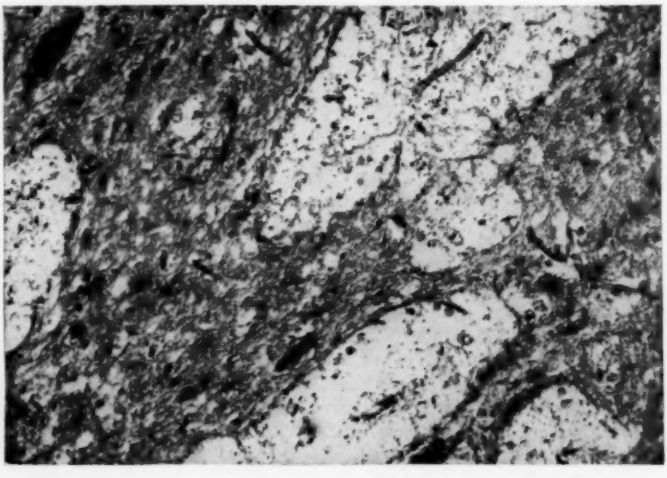


Fig. 2 (Case 1).—Section through area of histolysis in basal ganglia with typical soapsuds appearance. Hematoxylin-eosin stain; reduced to 61% of mag. × 75.

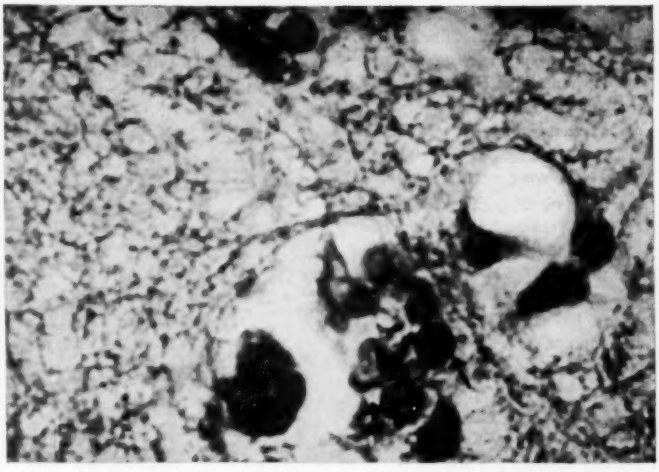


Fig. 3 (Case 1).—Section through lesion of histolysis in basal ganglia. Organisms are easily noted (arrows). P. A. S. stain; reduced to 61% of mag. × 900.

in his spinal fluid. He was sent to Michael Reese Hospital on April 22 for further study because of continuation of his headaches, fever, and diplopia, as well as the complaint of severe pain in his joints. The past history was irrelevant. There was no significant family history.

Physical and Laboratory Findings.—The blood pressure was 150/70. The temperature ranged from normal to 100.6 F. His face had a rounded appearance. The heart and lungs were normal. The liver was 3 fingerbreadths below the right costal arch in the midclavicular line. There were redness, swelling, heat, stiffness, deformity, and tenderness in almost all the joints. There was a mild degree of confusion regarding time and the significance of events in his illness. His speech was thick. There was atrophy of the small hand muscles (probably associated with arthritis). The tendon reflexes were generally brisk, and there were no pathologic reflexes. There was no objective diplopia, but the patient complained of blurring of binocular vision. Monocular vision was clear. There was no papilledema.

A detailed ophthalmological examination revealed an incomplete right third nerve palsy, and it appeared that the diplopia involved the third and fourth cranial nerves on the right side. The fields were normal.

The chest x-ray revealed a normal heart, but a distinct patch of infiltration was present in the posterior segment of the right lower lobe. X-rays of the various joints showed extensive rheumatoid arthritis involving the knees, hands, wrists, and acromioclavicular joints. The EEG was normal.

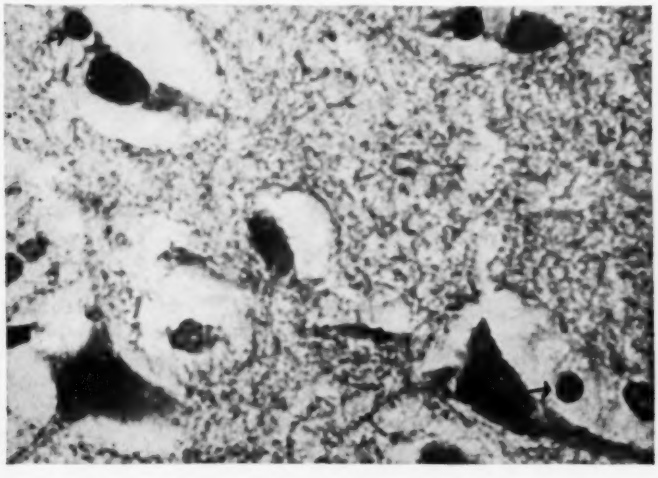


Fig. 4 (Case 1).—Basal ganglia, showing organisms (arrows) adjacent to ganglia cells. P. A. S. stain; reduced to 61% of mag. × 900.

L. E. preparations were negative. Routine blood studies were normal. The urine showed some yeast cells, but they were ignored at that time. Neurotropic virus studies on the same serum were negative for St. Louis encephalitis, western and eastern equine encephalomyelitis, lymphocytic choriomeningitis, and mumps. The heterophile and cold agglutinin tests were negative.

On April 25, 1954, the spinal fluid was clear and colorless and under a pressure of 146 mm. of water; Pandy 1+; 2 fresh red blood cells per cubic millimeter (97% lymphocytes and 3% large mononuclear cells); protein 99 mg/100 cc.; glucose 33 mg/100 cc.; chlorides 650 mg/100 cc.; Wassermann reaction negative; Lange curve 0000000000. No growth occurred in the culture in 72 hours, but after 10 days yeast colonies appeared for the first time. A second spinal puncture, done on April 30, showed similar findings. Again, after 10 days, the culture showed no pathogenic bacteria but yeast colonies were seen. The final report, on May 19, 1954, read: "A yeast morphologically and biochemically resembling Cryptococcus neoformans was isolated which is pathogenic for mice, producing fatal disease."

Course.—The patient was discharged on May 1, 1954, without much change in his condition. He was kept on corticotropin gel and hydrocortisone daily. There was no significant improvement. He continued to suffer fleeting and very occasional diplopia and frequent headaches.

Second Hospital Admission.—On Feb. 28, 1955, he was readmitted to Michael Reese Hospital for treatment of a chronic cryptococcic meningitis. The general physical examination revealed nothing significant aside from a blood pressure of 155/110 and the rheumatoid arthritis. There were no signs of meningeal irritation, and there was no objective impairment of eye movements. The general laboratory data of the blood and urine were not pertinent except that fungi were isolated from the latter. X-ray of the chest was normal. The spinal fluid was clear and colorless and under a pressure of 220 mm. of water, with 3 fresh red blood cells per cubic millimeter, 20 lymphocytes per cubic millimeter, a positive Pandy reaction, protein 102 mg/100 cc., glucose 1 mg/100 cc., and chlorides 731 mg/100 cc. After 48 hours, colonies of yeast were observed, which in six days were morphologically identified as C. neoformans. They were pathogenic for mice.

On March 5, 1955, cycloheximide therapy was started with 20 mg., given intravenously. Twenty minutes later he had severe projectile vomiting. The following day the patient was given 20 mg. of cycloheximide intravenously three times daily, the injections being carefully spaced so as not to interfere with meals, but each time he vomited violently. On March 7, a 20 mg. injection of the drug was given intramuscularly, with nausea as the only ill effect. That evening he became disoriented and disturbed and had urinary incontinence. A catheterized specimen of urine contained budding yeast cells, recognized in an India-ink preparation as C. neoformans (Fig. 5). Within the next two days the patient developed fever, with a temperature of 105 F rectally, with signs of pulmonary involvement, bilateral Kernig sign, nuchal rigidity, and bilateral Babinski sign. He lapsed into coma and died on March 10, 1955.

Autopsy.—Bacteriological studies were done shortly after death. Specimens from the following sites were positive for C. neoformans: spinal fluid, cisternal fluid, leptomeninges of the cerebral convexity, mediastinal and mesenteric lymph nodes, right lung lesion, and prostatic lesion. Specimens from spleen, bone marrow, and pericardial fluid were negative for growth.

The heart was grossly and microscopically normal. There was some slight atheromatosis of the ascending and descending aorta. The tracheobronchial and interbronchial lymph nodes were enlarged and anthracotic. The lungs contained some firm nodules, measuring 0.2×0.5 cm., at both bases; on section these were firm and grayish-white in appearance. In one area subpleurally, there was a large, irregular zone of necrotic material. In hematoxylin-eosin preparations this material stained brightly eosinophilic, and in it could be seen shadows of structures of numerous pale round bodies, measuring 3μ to 15μ, which in P. A. S. preparations stained faintly violet and were morphologically identified as C. neoformans. Near the periphery this necrotic material was surrounded by a well-defined wall, in which several zones could be made out. The innermost layer contained abundant nuclear debris; next was a zone with the ovoid organisms, and then an area of fibrotic granulation tissue, in which were many engorged capillaries, macrophages, lymphocytes, giant cells containing disintegrating cryptococci, and occasional plasma cells. Polymorphonuclear leucocytes were rare. This wall was surrounded by relatively normal lung. The bronchi were filled with thick mucus, containing polymorphonuclear leucocytes and some shadows of cryptococci. The liver, spleen, kidneys, alimentary tract, pancreas, bladder, and genitalia revealed nothing remarkable, either grossly or microscopically.

The prostate was enlarged, was of elastic consistency, and showed on section multiple confluent bright-yellow nodules. Microscopic sections revealed granulomas similar to those described in the lung section with cryptococci. The central necrotic area was surrounded by a dense cellular infiltrate of lymphocytes, plasma cells, and large multinucleated giant cells containing degenerated cryptococci.

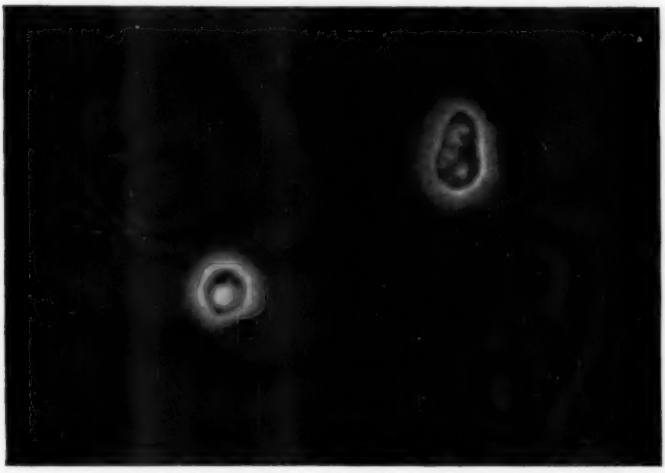


Fig. 5 (Case 2).—India-ink preparation of urine, showing budding C. neoformans in direct smear. Reduced to about 60% of mag. × 500.

The dura was normal, and the external surface of this brain was grossly normal except for some engorgement of the cortical veins, and possibly some slight thickening of the leptomeninges over the pons. Gross sections through the cerebellum and brain ganglia were normal. On the right there was an area of softening in the anterior part of the lenticular nucleus, measuring 2×3 cm. In the left side of the subependymal area near the anterior end of the lateral ventricle was another area of softening, measuring 3×1 cm., involving the body of the caudate nucleus, the anterior limb of the internal capsule, and the anterior end of the lenticular nucleus (Fig. 6). Neither of these areas had a honeycomb appearance, nor did they contain colloid material. Sections stained with hematoxylin and eosin and the P. A. S. method showed only a very mild cellular infiltration in the cortical meninges, consisting of lymphocytes and plasma cells. Sections through the intracerebral softenings revealed a similar state on the two sides, although more advanced on the left. There was a disintegration of the tissue, without the characteristic soapsuds appearance of cryptococcosis. On the right side, some part of the softened area was preserved and infiltrated with polymorphonuclear leucocytes and profusely scattered with gitter cells (Fig. 7). On the left, the dissolution was more complete, with gitter cells, lymphocytes, and plasma cells around the periphery and in perivascular spaces. The surrounding brain showed much perivascular edema. The P. A. S. stain showed no C. neoformans in this softened area (Fig. 8). Sections through the medulla showed mild meningeal infiltration with lymphocytes and

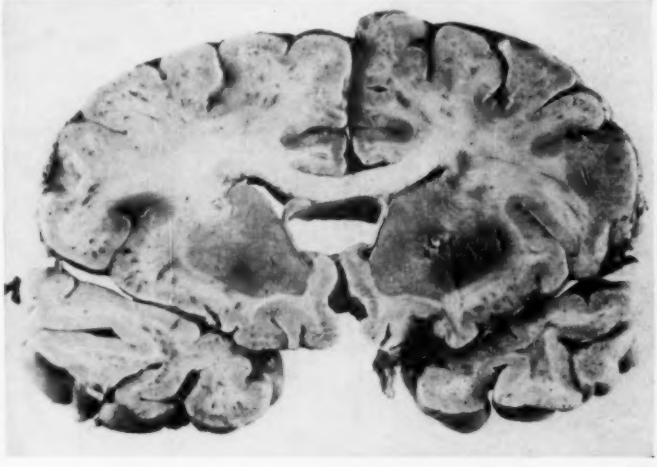


Fig. 6 (Case 2).—Gross brain section showing recent encephalomalacia and subsequent subependymal softening on the left.

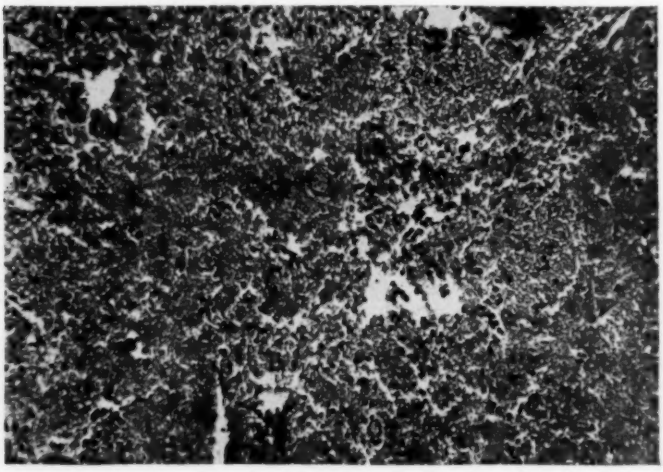


Fig. 7 (Case 2).—Softening in the right basal ganglia. Hematoxylin-eosin stain; reduced to 61% of mag. ×100.

plasma cells, as well as collections of cryptococci (Fig. 9). The choroid plexuses contained numerous cryptococci. The spinal cord was grossly normal. Microscopic studies revealed mild meningitis, consisting of infiltration with lymphocytes and plasma cells, with occasional C. neoformans scattered throughout.

Summary.—This patient was chronically ill with rheumatoid arthritis for three years (treated with corticotropin for two years), after which he developed mild meningoencephalitis, which was erroneously diagnosed as lymphocytic choriomeningitis. After about one year, it was found that this was due to C. neoformans. The patient remained in status quo for a period of about 10 months. He was rehospitalized and placed on cycloheximide therapy for three days. An acute exacerbation of his meningoencephalitis followed, and he died within one week. Pathologically, typical lesions of cryptococcosis were seen in the lung and prostate. The brain contained bilateral areas of encephalomalacia which did not look like cryptococcosis grossly or microscopically. There was a mild meningitis of the brain stem and spinal cord in which C. neoformans could be identified.

CASE 3.—Diagnosis: Cryptococcosis (courtesy of Dr. I. U. Spiegel).

A 43-year-old white man was admitted to Michael Reese Hospital, Chicago, on June 26, 1954, because

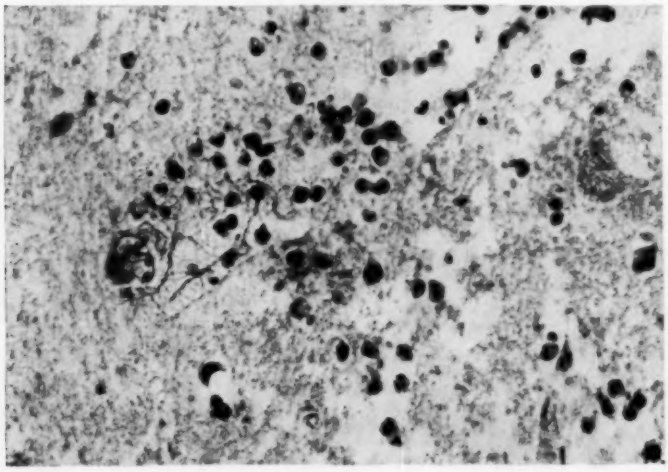


Fig. 8 (Case 2).—Softening in right basal ganglia, showing polymorphonuclear leucocytes, gitter cells, but no organisms. P. A. S. stain; reduced to 61% of mag. × 500.

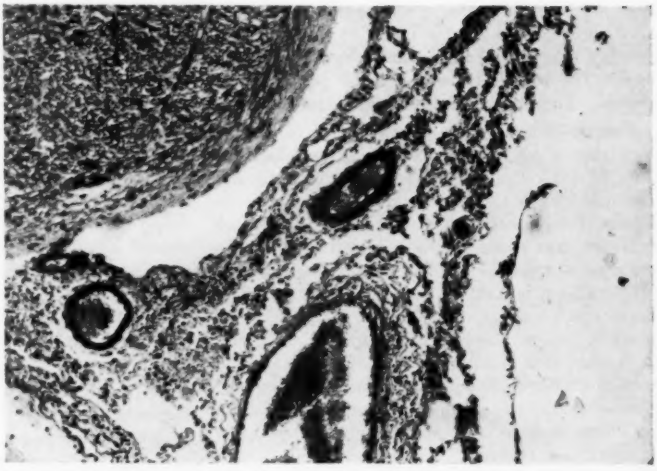


Fig. 9 (Case 2).—Meninges of medulla, revealing meningitis. P. A. S. stain; reduced to 61% of mag. × 100. In higher magnification the cryptococci could be recognized easily.

of severe headache, projectile vomiting, and increasing drowsiness for three days.

History.—The only relevant antecedent history was that he had had meningitis at the age of 2 years, without known sequelae. He had been living and working in and around Chicago throughout his adult life.

About one week before admission to Michael Reese Hospital, on June 26, 1954, while working in his basement, the patient hit his head on a low beam. This stunned him momentarily, and the incident was then forgotten. The next day he began to suffer from headaches of increasing intensity. For three days prior to hospitalization, he was quite ill, with severe headache, projectile vomiting, confusion, and fluctuating stupor.

Physical and Laboratory Findings.—When admitted, the patient was stuporous and incoherent. The blood pressure was 146/70. The temperature fluctuated between 99 and 100 F. Several small bubbling bronchial rales were found in both lung bases posteriorly. The heart and abdomen were normal. Both pupils were miotic but responded to light. There was severe papilledema bilaterally. The neurological examination was otherwise negative.

Skull x-rays were normal. The chest x-ray showed no definite evidence of infiltration, but there was a linear strand in the left lung base which was considered to represent an old area of focal atelectasis. The heart was normal. An electroencephalogram was done on June 29, 1954, and was

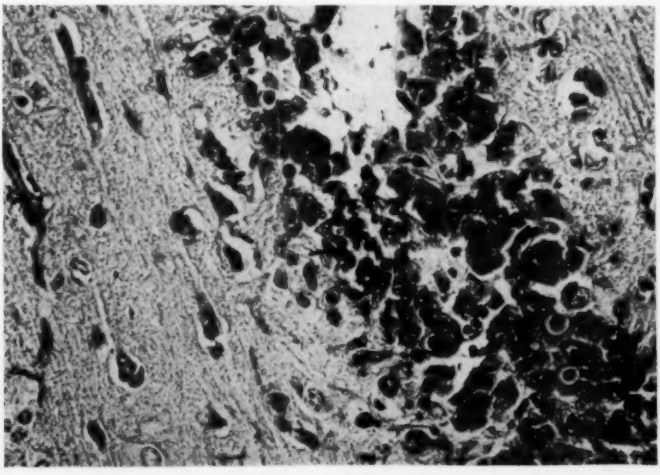


Fig. 10 (Case 3).—Biopsy of leptomeninges. Meningitis and organisms easily seen. Arrows point to organisms. P. A. S. stain; reduced to 61% of mag. × 500.

reported as: "No localizing or lateralizing changes; slow abnormality seen, but not of a severe degree, possibly suggesting predominant subcortical pathology." The routine urine and blood profiles were normal. The blood Kahn test was negative.

Course.—Because of the papilledema without localizing signs, a ventriculogram was done on June 29, 1954. Difficulty was encountered in finding the ventricles, but when they were entered, a fresh bloody fluid escaped under seemingly increased pressure from both sides. The ventriculogram was essentially normal. For relief of pressure, this was followed by a right subtemporal decompression. The brain was found to be under markedly increased pressure, and the bulging was extremely jelly-like. A nodular area of pathology presented itself in the meninges and was removed for biopsy (Fig. 10). The microbiology laboratory found no organisms on direct smear of the ventricular fluid, but a 48-hour culture suggested the possibility of C. neoformans. The biopsy was later reported by the pathologist as showing C. neoformans.

Within the next 24 to 48 hours the patient became worse. His face became edematous. He was stuporous, and marked nuchal rigidity had developed. There was quadriparesis with hypertonus on the right and flaccidity on the left. There was bilateral papilledema. Pinprick perception was intact. At this time the spinal fluid was xanthochromic, and the pressure was 450 mm. of water. A direct India-ink preparation of the spinal fluid revealed large encapsulated and budding yeast cells morphologically resembling Cryptococcus.

On July 5, 1954, cycloheximide therapy was started. He was given 20 mg. intrathecally, and this was repeated on July 6, 12, 16, and 21, for a total of 100 mg. Cycloheximide was also given intravenously, starting with 60 mg. daily (20 mg. three times daily) and increasing to a maximum of 20 mg. daily over the ensuing 28 days for a total of 3549 mg. He was also given penicillin, dihydrostreptomycin, chlortetracycline (Aureomycin), and sulfadiazine for varying periods of time. In addition, the usual supportive measures were used. For five days he was given 150 mg. of cortisone daily about a week prior to death. His condition gradually worsened, and the temperature fluctuated between 99 and 105.2 F. A tracheotomy had to be done to facilitate breathing. Gradually, coma deepened, and the patient died, on July 30, 1954.

Further Laboratory Data.—On July 6, the bacterial agglutinations were all negative. Viral complement fixation tests, neurotropic virus studies, and heterophile antibodies were all negative. Subsequent spinal punctures made on July 6, 12, 20, and 21 revealed increased pressures, and all revealed positive cultures in 48 hours for C. neoformans. A blood culture done on July 22 was later reported as growing hemolytic (coagulase-positive) colonies.

Autopsy.—The lungs, heart, liver, spleen, alimentary tract, pancreas, kidneys, bladder, prostate, testes, and lymph nodes revealed nothing remarkable either macroscopically or microscopically. The adrenals were symmetrical. The corticomedullary junction was slightly obliterated by some grayish-light-brown lesions. The cortex was mottled by deep-yellow areas on section. One of the adrenals showed large foci of necrosis in the medulla. Surrounding the necrotic centers were lymphocytes, necrotic debris, and masses of cryptococci showing occasional budding. There was no fibrous and very little cellular reaction. There were smaller similar foci in the cortex.

Brain.—In the region of the right temporal lobe, the necrotic herniated brain was seen at the site of the decompression. The cortical vessels were hyperemic, and the subarachnoid space was distended. Through the meninges, a number of flat nodules, less than 1 mm. in diameter, were noted. They were most evident in the right parietal region and in the left Sylvian fissure. Cross sections of the brain revealed, in the basal ganglia, especially in the lenticular nuclei and adjoining capsules, a number of small, ill-defined cavities containing a gelatinous material and giving the appearance of a honeycomb (Fig. 11). Microscopic sections studied with hematoxylin and eosin and P. A. S. stains revealed that the subarachnoid spaces contained dilated vessels, a mild lymphocytic infiltration, and numerous C. neoformans organisms lying free and within capillaries. In sections of the cortex there were various-sized cavities containing a small amount of fibrin and some necrotic debris, with cryptococci profusely present, some of which showed budding forms. The same was true of the lesions in the basal ganglia; only the honeycomb cavities were larger. In some sections these lytic lesions were in the perivascular spaces. There was remarkably little cellular reaction around these cavities.

Summary.—This patient's illness started with a mild head injury, and within one week he had a marked increase in intracranial pressure without localizing signs. The diagnosis was made following ventriculography, by culture of the spinal fluid, and by biopsy of the meninges. Subsequently repeat cultures of the spinal fluid were positive for C. neoformans. The patient was treated intensively with cycloheximide, but this did not materially affect his illness, and he died on July 30, 1954. The autopsy revealed only one focus of cryptococci outside the nerv-

ous system and that was in one adrenal gland. Otherwise, there was a typical convexity granulomatous meningitis and an intracerebral cryptococcosis. In both locations C. neoformans was evident.

Comment on Cases of Cryptococcosis

A rather complete clinical and pathologic picture of this disease complex as it affects the central nervous system has been summarized excellently by Mosberg and Arnold.[14] Each of the three cases in our group demonstrates a different, yet frequently reported, type of onset. Case 1 had a known diagnosis of Hodgkin's sarcoma for a period of at least three years. The combination of these two conditions has often been recorded (Gendel[15] and Rodger[16] and their associates). The most plausible explanation is that this fungus disease is more prone to develop in a person with poor or lowered resistance. Perhaps it can be postulated that any central nervous system complication in a prolonged chronic illness should immediately raise the question of fungus superinfection, especially cryptococcosis, seen not only in Case 1, but also in Case 2, where for two years there was a preexisting rheumatoid arthritis. It must be mentioned, too, that cryptococcosis has been seen coexisting in conditions of malignant lymphomas (Collins and associates[17]), in endocarditis, pyelonephritis, and diabetes, and even in conjunction with other fungus infections (Rodger and associates,[16] Zimmerman and Rappaport[18]).

There are numerous reports of cases of cryptococcosis in which the disease has been incorrectly diagnosed as some form of chronic meningitis, notably tuberculous or even choriomeningitis, as in Case 2, on evidence of inadequate spinal fluid examination. All three conditions may reveal a pleocytosis and elevated protein content, and often a decreased glucose and chloride content. In our Case 2, the diagnosis of lymphocytic chorio-

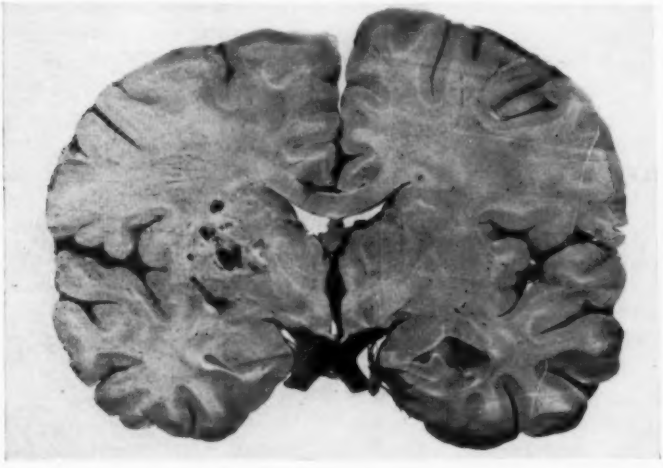


Fig. 11 (Case 3).—Gross sections of brain—honeycomb lesions in the basal ganglia.

meningitis was assumed because of nonspecific spinal fluid findings. Such a diagnosis should not be accepted without at least the demonstration of a significant increase (fourfold) in neutralizing or complement-fixing antibodies against the specific virus in the acute and convalescent phases. The mere presence of such antibodies is not diagnostic, because they may be due to past infection. Similarly, tuberculosis should not be accepted as a final diagnosis until the tubercle bacilli are demonstrated, or at least until fungus disease has been excluded.

In Case 3 there is demonstrated another group of diagnostic difficulties. There are numerous cases of cryptococcosis on record in which a marked increase of intracranial

pressure has raised the question of a space-occupying lesion. In fact, some cases are recorded of an actual space-occupying lesion produced by a granuloma composed of organisms. Usually the history is that of apparent good health until the time of a relatively mild cranial injury, when there is the picture of an acute increase in intracranial pressure. A subdural hematoma may be suspected. Wilson and Duryea [19] reported such a case. Martin and Podberg [20] have reported a similar experience. As in their cases, our experience was with a patient who had no localizing signs, yet there was a progressive hemiplegia. In many such cases burr holes have been made in search for a hematoma. Actually, the diagnosis in our instance was made by culture of the ventricular fluid and by biopsy of a granulomatous lesion in the meninges. We could speculate that such a patient may have had a focus of cryptococci elsewhere in the body and only after the head injury did the brain become a locus minoris resistentiae. The other organ found to contain the fungi was one adrenal gland. It would be most likely to assume that this was not the primary site, and perhaps the portal of entry of the organisms was missed at autopsy or had healed.

That cryptococcosis can resemble and act as a spinal cord lesion has been reported by Ley and associates,[21] who removed a Torula granuloma from the cervical cord an 8-year-old girl.

The diagnosis of cryptococcosis is not too difficult provided it is entertained as a possibility in cases of acute or chronic meningoencephalitis of unknown etiology. The organism can often be recognized in spinal fluid directly by India-ink preparation (Weidman and Freeman [22]), or it can be grown readily on Sabouraud's glucose agar at room temperature and at 37 C. In primary cultures the colonies of C. neoformans usually appear in two to four days. However, one should retain the culture for at least 30 days before considering it as sterile (Smith [23]).

Heretofore, many types of management have been used in cryptococcosis, but all to no avail. Since some patients may die during a fulminating stage or may live for more than nine years in chronic invalidism, with periods of relative quiescence, the value of any particular therapy is difficult to assess. Wilson and Duryea [19] used cycloheximide, a new antibiotic, in their case, utilizing 40 to 60 mg. intravenously daily for about 18 months. Intrathecal use of the drug was discontinued when their patient developed lethargy, ataxia, and slurred speech. A sterile spinal fluid and a clinical arrest in an apparently progressive case were achieved. These observers demonstrated that the drug does reach the spinal fluid. Recently, Currier * reported to us a case of cryptococcosis with a blood dyscrasia in which the patient apparently is improving on cycloheximide therapy. On the other hand, other reports are not too encouraging, even though it is generally agreed that the drug is effective in inhibiting the growth of the organism in vitro (Carton,[12] Haspel and associates,[24] and Kligman and Weidman [25]).

Our three cases were treated with cycloheximide, in addition to other antibiotics. Case 1 received 6590 mg. intravenously in over 55 days (minimal dose 20 mg. daily to a maximum of 200 mg. daily, except for 300 mg. on one day) and 60 mg. intrathecally in 9 doses (2 doses of 10 mg. and 7 doses of 20 mg.). This case was chronically progressive and seemed uninfluenced by the drug. In Case 2 the disease was static, with moderately severe symptoms for almost two years, when he was brought to the hospital specifically for the cycloheximide therapy. He received 20 mg. intravenously for the first day and in 20 minutes had severe projectile vomiting. The second day he received 20 mg. intravenously on three occasions, spaced so as to avoid meals, and each time he vomited. The third day 20 mg. was given intramuscularly, and the only ill effect was nausea. The evening of the third day he became disoriented, and cycloheximide was stopped. Within the next few days the course was rapidly downhill, with increasing meningoencephalitic signs, and the patient died. The conclusion is inescapable that

* Currier, F. P.: Personal communication.

cycloheximide appeared to precipitate the patient's death. The lesions in the brain were fresh softenings, with no invasion by C. neoformans, and did not have the gross or microscopic appearance of cerebral cryptococcosis. Still, there could be little doubt that the patient had cryptococcic meningitis. Case 3 suffered an acute cryptococcosis of the brain. Within 28 days he received 3540 mg. of cycloheximide intravenously (minimum daily dose of 200 mg.) and 40 mg. intravenously in two doses. The disease process was apparently uninfluenced by the drug therapy.

COCCIDIOIDOMYCOSIS

CASE 4.—Diagnosis: Coccidioidomycosis. (This case was furnished us through the courtesy of the Veterans Administration Research Hospital, Chicago, service of Dr. Roy Whitman. It will be reported in detail by Dr. Whitman and staff in the future.)

A 26-year-old white man was transferred to the Veterans Administration Research Hospital, Chicago, on June 19, 1954, from the Veterans Administration Hospital, Danville, Ill., where he had been treated for several months for a chronic infection of the respiratory and central nervous systems.

History.—The patient was stationed in California during part of his Navy service in World War II and, subsequent to that, had worked at odd jobs in California and Arizona during the year of 1952. His illness began with pain in the right thorax in the spring of 1953. He developed a chronic cough and hemoptysis. In March, 1954, he had fever, headaches, malaise, nausea, and vomiting. While at the Veterans Administration Hospital in Danville, he had nuchal rigidity and auditory disturbances. In this condition he was transferred to the Research Hospital in Chicago on June 19.

Physical and Laboratory Findings.—On admission he did not appear acutely ill. His blood pressure was 110/60. There were tubular breath sounds over the left lung base posteriorly. The heart was normal. The abdomen was normal except for a palpable spleen. The neurologic examination was negative, and no nuchal rigidity was detected. X-ray of the chest revealed two large cavities adjacent to the hilus. The sputum was highly suggestive of C. immitis. The urine was normal. The hemogram showed 5400 W. B. C. per cubic millimeter, with a normal differential count. Hemoglobin was 12.5 gm/100 cc.; sedimentation rate, 16 mm. in one hour; the VDRL test was negative. Liver function tests were normal. The blood urea nitrogen was 12 mg/100 cc. On Feb. 28, 1954, the spinal fluid was under a pressure of 280 mm. of water, containing 428 cells (5% polymorphonuclear leucocytes and 95% lymphocytes) and 38 mg. of sugar, 240 mg. of total protein, and 100 mg. of chlorides, per 100 cc., and gave a 4+ Pandy reaction. The coccidioidin skin test was negative. A serum specimen was sent to Stanford University School of Medicine on June 9 and was reported as positive (4+) in 1:32 dilution for coccidioidal complement fixation. No organisms were seen on direct smear of the spinal fluid, and the culture was sterile.

Hospital Course.—On July 12 treatment with 2-aminostilbamidine was started. He received 150 mg. daily for three days and 200 mg. daily thereafter, diluted in 200 cc. of isotonic saline, intravenously. This was continued for a total of 6 gm. for about one month. Renal and hepatic function remained normal. Recheck of the spinal fluid showed normal pressure, with other findings relatively unchanged except for an increase in protein to 840 mg/100 cc. A serum specimen drawn on Aug. 31 was reported by the Stanford University School of Medicine as positive (4+) in a dilution of 1:32, and the spinal fluid drawn at the same time was reported as showing a positive (3+) complement fixation in a dilution of 1:256. A precipitin test of the spinal fluid was positive in a dilution of 1:40. The Stanford University Laboratory indicated that these findings established the diagnosis of coccidioidal infection in the central nervous system.

He was placed on 2-aminostilbamidine, 200 mg. daily for several weeks to a total of 10 gm. In September, 1954, he was sent home on a leave of absence for 30 days and while there developed progressive weakness and numbness of both lower extremities. On his return to the hospital, a lesion was localized clinically at the fourth thoracic dermatome. Myelography revealed a block at the 10th thoracic dermatome. A laminectomy was done on Oct. 14, and a very thick arachnoid was found completely encircling the cord and extending throughout the field. A biopsy specimen was taken. The patient seemed to be recovering well from surgery for about an hour, after which he went into profound shock and respiratory failure, and, in spite of intensive supportive measures, he died, on Oct. 16.

The biopsy tissue from the arachnoid was later reported as revealing C. immitis.

Autopsy (courtesy of Dr. A. A. Teloh, Veterans Administration Research Hospital, Chicago).—The heart was quite normal except for a rare soft, atheromatous plaque on the intima of the coronary arteries. There were no significant microscopic changes. Evidence of bronchopneumonia was present in the upper and lower lobes of the right lung. The thyroid and lymph nodes were essentially normal except for some hyperemia. The liver and gall

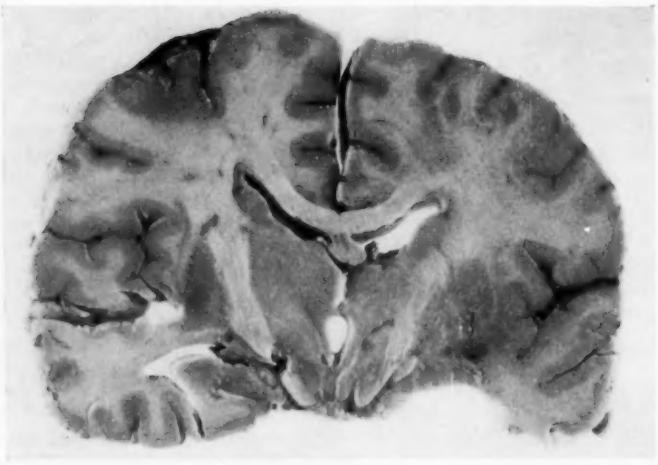


Fig. 12 (Case 4). — Gross brain section, showing basilar meningitis.

bladder were normal. The spleen was hyperemic but otherwise normal. The pancreas was normal. The gastrointestinal tract was normal. The adrenal glands were normal. The genitourinary system was normal. The brain was under increased pressure, with flattened gyri. There was a greenish plastic exudate, about 1 mm. in thickness. This extended forward to obscure the interpeduncular area (Fig. 12). The ventricular system was moderately dilated. The choroid plexuses contained a greenish exudate. The lining of the third ventricle was roughened. There was no evidence of intracerebral pathology. The entire extent of the spinal cord was covered with a thick, greenish-white membrane, measuring 3 mm. in thickness at the upper levels of the cord, and this lay intradurally (Fig. 13). The dura itself seemed normal. On section, the cord was seen to be soft in consistency.

Sections of the brain were studied with hematoxylin-eosin, P. A. S., Weigert, Van Gieson, and Weil stains. The dorsolateral meninges showed a mild inflammatory reaction, with lymphocytes and plasma cells near the large vessels. There was a moderate increase in fibrous tissue in the meninges. No fungi or giant cells could be seen there. The cortex itself was free of abnormalities. Sections through the basal ganglia and the lateral ventricles showed a normal ventricular lining and no changes in the basal ganglia. Sections taken through the floor of the third ventricle to include the thick exudate described on the base of the brain showed a marked granulomatous meningitis. The meninges were thick and contained numerous tubercle-like structures (Fig. 14). There were numerous large giant cells with many nuclei. Often these giant cells were surrounded by a clear area of fibrous

Fig. 13 (Case 4).— Gross sections of brain stem and spinal cord, showing thick leptomeningitis.

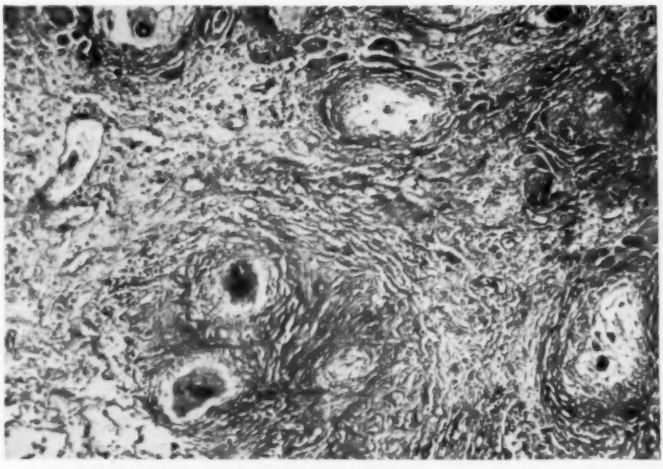


Fig. 14 (Case 4).—Basilar meninges. Tubercle-like structures containing large giant cells in which are seen C. immitis. P. A. S. stain; reduced to 61% of mag. × 125.

tissue, and surrounding this was a conglomeration of lymphocytes and plasma cells. This inflammatory reaction projected up into the third ventricle like a cauliflower. In places, the lining of the third ventricle was destroyed. The whole area had a profusion of dilated blood vessels. In the hematoxylin-eosin preparation could be seen an occasional giant cell, within which was a highly refractile, rounded area without any significant content. With the P. A. S. stain these areas revealed spherical organisms morphologically recognized as C. immitis. They varied from 20μ to 60μ in diameter and stained dark red. In many organisms could be seen endospores. Some were very large cells full of endospores which seemed ready to burst. Only in isolated instances did it appear that such organisms were seen apart from giant cells.

In the levels examined, the spinal cord showed disintegration of its posterior two-thirds, with beginning destruction of myelin and no intramedullary inflammation. The thick exudate already described grossly showed the same general form as at the base of the brain (Fig. 15). Organisms morphologically recognized as C. immitis were seen in giant cells singly or in groups of up to four or five (Fig. 16).

Summary.—The illness started with respiratory disease. Within a year the patient developed evidence of meningoencephalitis. A positive culture of C. immitis from the sputum suggested the possibility of coccidioidomycosis. Complement fixation studies on the blood and spinal fluid, as well as the

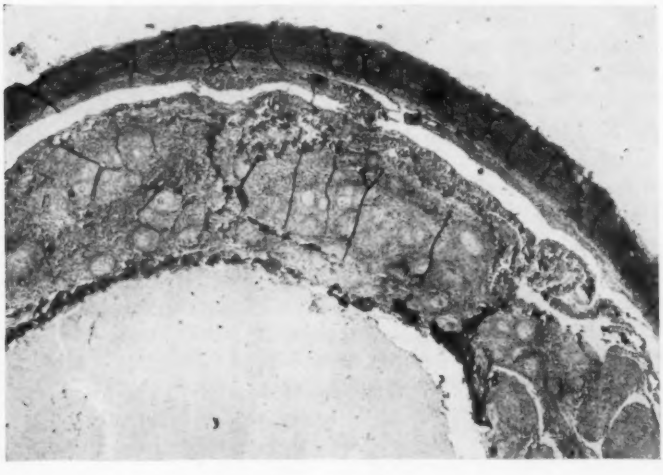


Fig. 15 (Case 4).—Spinal cord granulomatous meningitis with softening. Van Gieson stain; reduced to 61% of mag. × 25.

precipitin test on the spinal fluid, proved the diagnosis serologically. There then developed a picture of a transverse cord lesion. Exploratory laminectomy revealed a granulomatous leptomeningitis, and biopsy of this showed C. immitis. The patient died about one and a half years after the onset of his illness. The autopsy revealed a severe basilar and spinal granulomatous leptomeningitis in which C. immitis was identified. No evidence of fungus infection of the lungs was found, for this had apparently cleared up before death.

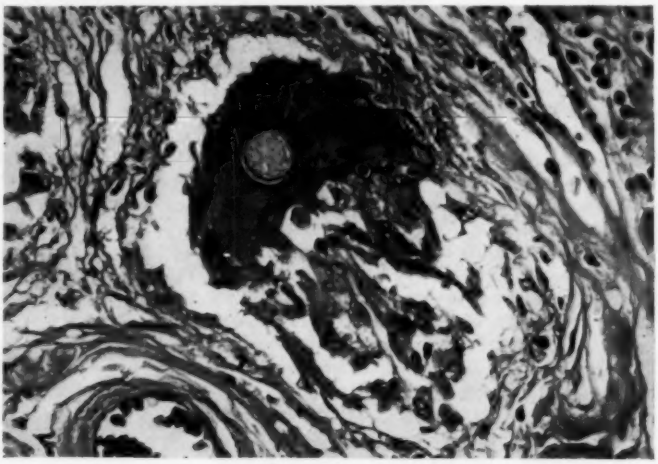


Fig. 16 (Case 4).—Spinal meninges. Giant cell containing C. immitis. Hematoxylin-eosin stain; reduced to 61% of mag. × 500.

Comment on Coccidioidomycosis

When coccidioidomycosis invades the central nervous system, it is the result of dissemination of infection from a primary site, which is nearly always in the lung. This illness is usually fatal. Forbus,[26] in a large series of cases, reported that 10% had nervous system involvement confined to the meninges. Schlumberger [27] noted an incidence of 13 cases of basilar meningitis in 23 cases of disseminated coccidioidomycosis studied at the Army Institute of Pathology. On the other hand, Abbott and Cutler [28] reported an incidence of 25%. It should be remembered that the primary site of entry may escape detection even at autopsy, so that only central nervous system involvement is obvious; this was true in our case.

The disease produces a thick fibrous meningeal exudate around the base of the brain, giving a clinical picture of meningoencephalitis or even a neoplasm (Jenkins and Postlewaite [29]). At times the granuloma may even resemble a cord tumor (Rand [30]). The combination of the two symptoms complexes may be seen, as it was in our case. The organism C. immitis was easily identified in the tissue with the P. A. S. stain.

The clinical diagnosis is dependent upon a healthy suspicion and awareness. In most instances no organisms can be identified from the fluid on either smear or culture, but complement fixation and precipitin studies on the serum and spinal fluid are diagnostic.

Death usually occurs within four or five years, although a case of survival for 10 years is on record, without any specific treatment (Norman and Miller [31]). Our patient received 10 gm. of 2-aminostilbamidine in doses of approximately 200 mg. intravenously on a daily basis. He tolerated medication well, and it appeared that he was doing satisfactorily, when rapid progression of his spinal granulomatous meningitis led to his death. There can be no claim that this drug did the patient any good, in the face of such progression. Stilbamidine (Christison and Conant [32]) has been effective in vitro against blastomycosis and cryptococcosis, and clini-

cally some claims have been made for its use in the therapy of coccidioidomycosis. Jenkins and Postlewaite [29] employed cycloheximide in two cases of this fungus involvement, and one of the patients who survived was given doses of 300 mg. intravenously, with only one disagreeable symptom of disorientation. The other patient who died received two courses of cycloheximide, one of 400 mg. and the other of 320 mg. The patient developed urinary incontinence plus mental symptoms of disorientation. Death occurred nine months after therapy was instituted, and the pathology was typical for coccidioidomycosis.

ASPERGILLOSIS

CASE 5.—Diagnosis: Aspergillosis (courtesy of Dr. Raphael Isaacs).

A 23-year-old white woman was readmitted to Michael Reese Hospital on Sept. 6, 1953, because of confusion, lethargy, and a 25 lb. weight loss in the previous six months.

Past History.—In February, 1953, the patient complained of menorrhagia and metrorrhagia over a three-month period. In April, because of this, she underwent a dilatation and curettage and later received three blood transfusions. In May, 1953, because of weakness, headaches, dizziness, dyspnea, blurring of vision, bleeding gums, and normochromic anemia, she was given six more blood transfusions. Despite these measures, hemoglobin failed to rise, and the patient was then placed on corticotropin in increasing doses. All told, she received a total of 18 blood transfusions during three periods of hospitalization. In August, 1953, the patient was hospitalized elsewhere because of an infected cut finger, the lesion requiring excision and drainage. Cultures revealed hemolytic staphylococci. She was treated with penicillin, polymyxin B topically, and sulfadiazine. During this same hospital admission the patient experienced a major convulsion and began to suffer severe generalized pounding headaches, which persisted until after her discharge. Changes in her memory were soon noticed, but she was still able to carry on her household duties. The first admission to Michael Reese Hospital was on Aug. 28, 1953, when she was discharged without a definite diagnosis. Some consideration, however, was given to the possibility of an unusual type of leukemoid reaction. At various times during the preceding six months she had received a total of 1225 units of corticotropin. The patient did not improve after discharge and was readmitted four days later, on Sept. 6, 1953, in a very confused state, with severe headache, nausea, and vomiting. In all, she had lost 25 lb. in the past six months.

Physical and Laboratory Findings.—Pulse 110; respiration 16; blood pressure 106/70, and temperature 101 F. The patient at times appeared mentally clear, presenting a fairly systematic account of her illness; but at other times she became very infantile and only echoed questions and directions. She would become disoriented and noisy. She was quite pale, and there was a follicular rash with some vesicles over the chest, shoulders, and face. Small lymph nodes were palpable in the cervical and axillary regions. White plaques were seen on the buccal mucosa and tongue and over the tympanic membranes. The thyroid was slightly enlarged and multilobular. There were decreased breath sounds and dullness in the right lower lobes posteriorly. The heart was not enlarged. A Grade 2 systolic murmur was present over the pulmonic area. The liver and spleen were just palpable. The neurologic examination revealed a positive left Oppenheim sign, bilateral ankle clonus, brisk tendon reflexes, normal sensation, and intact cranial nerves except for some blurring of the disc margins, particularly on the nasal side. The blood and urine studies were normal. The chest x-ray revealed diffuse mottling with nodular densities through both lung fields. An EKG was suggestive of myocarditis and pericarditis.

Hospital Course.—The patient continued to be confused and irrational during most of her hospital stay and ran a febrile course ranging from 98.6 F, orally, to 108 F, rectally, just before she died. A lesion which looked like an infected sebaceous cyst was found on the scalp and removed. Microscopic examination of this tissue revealed C. albicans. A throat culture revealed Gram-positive bacilli. Spinal punctures were done on Sept. 11 and Sept. 21, 1953, with the following results: The maximum pressure was 300 mm. of water. The first fluid was cloudy and blood-tinged (traumatic), containing 5986 fresh red cells per cubic millimeter (12 lymphocytes and 2 polymorphonuclear leucocytes), with 2+ Pandy reaction, and 58 mg. of glucose, 20 mg. of protein, and 667 mg. of chlorides, per 100 cc. The second fluid was clear and colorless with 23 fresh R. B. C., 9 W. B. C. (6 polymorphonuclear leucocytes and 3 lymphocytes) and 54 mg. of glucose, 68 mg. of protein, and 655 mg. of chlorides, per 100 cc. No organisms were seen on direct smear or after culture of the spinal fluid for 30 days. Cultures of the throat, tongue, buccal mucosa, and urine were positive for C. albicans. Aspergilli were isolated from two urine cultures. The blood culture was negative. On Sept. 24 the patient was placed on isoniazid and potassium iodide. On Sept. 26 she had slight nuchal rigidity and later became comatose. She received one dose of methylrosaniline chloride intravenously. During this final period of

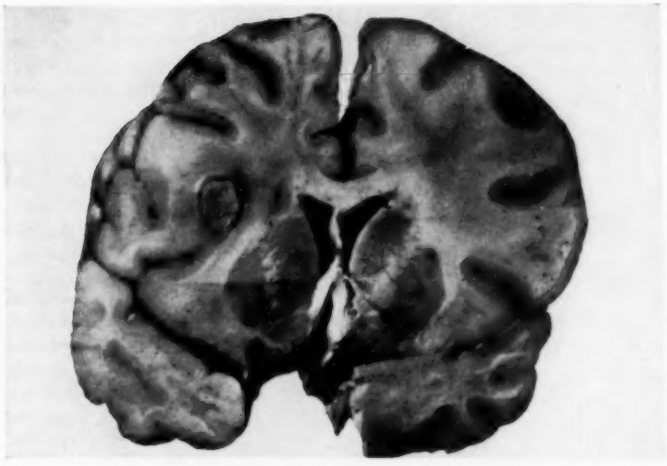


Fig. 17 (Case 5).—Gross section with Aspergillus abscess.

hospitalization she received only 125 units of corticotropin gel in all. The patient died on Sept. 28, 1953.

Autopsy.—There was diffuse involvement of the heart, posterior trachea, and lung. Cultures from these abscesses were positive for Aspergillus. The bone marrow and lymph nodes showed no evidence of leukemia.

The internal surface of the dura near the sagittal sinus contained a number of yellowish nodular lesions. The meninges were thickened and diffusely granular, especially in the interpeduncular area. Sections through the brain revealed several small and large abscesses throughout (Fig. 17). In the left frontal lobe there was a focus of hemorrhage, measuring 1.5×2.5 cm. The largest abscess was in the region of the occipital lobe, involving primarily the white matter and only part of the adjacent cortex and measuring 1.5×2 cm. The center of this was necrotic. There were smaller abscesses adjacent to this larger one. A large abscess was found in the right cerebral peduncle. Microscopically, the lesions in the brain were essentially similar to those in the other organs. However, there were many spores and some vascular invasion by fungi (Figs. 18, 19, and 20).

Summary.—This patient became ill with excessive uterine bleeding. She was treated with corticotropin for six months. Subsequently she developed meningoencephalitis. No organism could be cultured from the spinal fluid. At autopsy there was found diffuse involvement of various tissues with

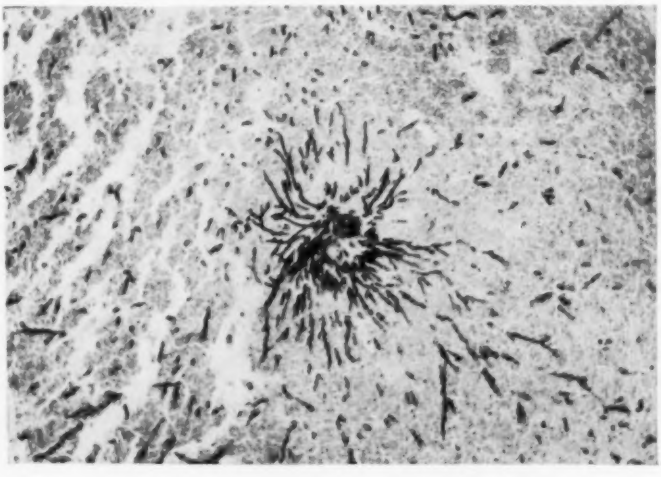


Fig. 18 (Case 5).—Small Aspergillus abscess in cerebrum. Hematoxylin-eosin stain; reduced to 61% of mag. × 125.

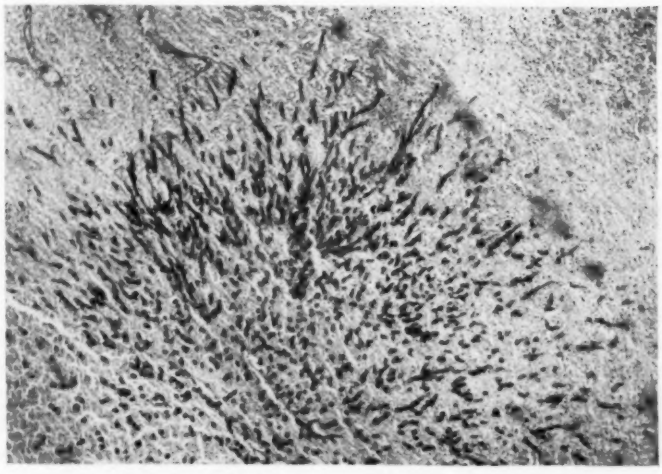


Fig. 19 (Case 5).—Section through abscess in cerebrum. P. A. S. stain; reduced to 61% of mag. × 125.

Aspergillus. The brain contained numerous abscesses with a profusion of aspergilli. There also appeared to be a systemic infection with C. albicans, but there was no evidence that this involved the central nervous system. This was considered as a possible secondary invader.

Comment on Aspergillosis

Cases of cerebral aspergillosis have rarely been recorded. Since the first report by Egas Moniz and Loff,[33] of a frontal lobe abscess due to Aspergillus, there have been only a total of nine cases involving the central nervous system, and these were in the form either of an abscess or of granulomatous meningitis. There are perhaps some seven other cases which involved the nervous system as a result of spread from adjacent bone or of systemic infection. However, none of these cases are well authenticated. In the most recent available reports, two cases are recorded, one in a 26-year-old soldier in which the disease behaved like a posterior fossa tumor, but pathologically proved to be a severe basilar and spinal granulomatous meningitis with an abundant growth of A. fumigatus from the subarachnoid exudate. The other was that of a 10-month-old infant with a picture of basilar meningitis, which

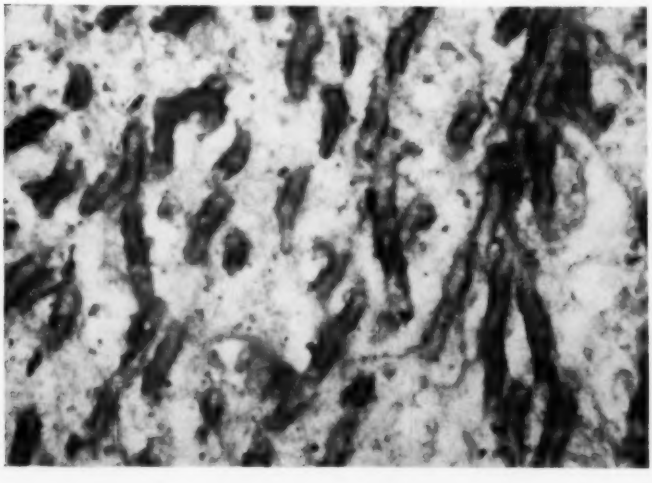


Fig. 20 (Case 5).—Aspergilli in brain abscess, showing septa. P. A. S. stain; reduced to 61% of mag. × 500.

pathologically revealed many granulomas in the cortex (Iyer and associates [34]).

Our case was that of some type of chronic disabling disease with menorrhagia and metrorrhagia which was suspected of being leukemia, but this was disproved. She was treated with corticotropin for about six months. Later she suffered a cut finger, which failed to heal, and a chronic meningoencephalitis thereafter developed, of which she died. The autopsy and bacteriological studies suggest a joint infection with C. albicans and aspergillosis. However, the latter was a disseminated process, involving many tissues and producing multiple granulomatous abscesses throughout the brain. Aspergilli could be identified and cultured. This diagnosis is a difficult one to prove because ante mortem the various body secretions may be easily contaminated with Aspergillus infection by the usual course of events in a chronically debilitated person; but there can be no doubt in our case.

GENERAL COMMENT

The appearance of five cases of fungus infections of the central nervous system in so short a period of time in an area where such cases have been relatively infrequent bears some comment. The case of coccidioidomycosis is easy to explain, since the patient worked in a known endemic area. However, the diagnosis had to be made in an area far removed, where such diseases are quite rare. The migratory nature of our population can spread such cases to unsuspecting localities. Regardless of this, such an explanation is inadequate for the three cases of cryptococcosis and the one case of aspergillosis. Although our experience suggests it, we can only hint that such cases are on the increase. A perusal of the literature, especially in relation to cryptococcosis of the nervous system, would certainly support this view. Mosberg and Arnold [14] pointed out that prior to 1946 there were 108 cases on record and from 1946 to 1949 there were reported 64 cases. Undoubtedly, a good part of this apparent increase must be due to better diagnosis, but the question must be raised as to whether there is some alteration in the virulence of the infection or the resistance of the host to explain this.

The present ubiquitous use of antibiotics, corticotropin, and cortisone has produced considerable comment regarding the role these substances may play in this regard. There are a few reports in the literature in which the prolonged use of antibiotics has been indicated for the rapid dissemination of fungus infections (Zimmerman,[35] Hutchison,[38] and Reiches [39]). In discussing the question, Kligman [40] urges caution in such a conclusion. There is no convincing evidence that antibiotics directly stimulate the growth of fungi. He does not feel that superinfection of this type is common, but when it does occur, it is a more serious problem with bacterial infections due to organisms such as coagulase-positive Staphylococcus and hemolytic Streptococcus than with fungi. He suggests that such fungi, which ordinarily have low virulence, may become invasive when the host defenses are depressed by prolonged serious illness. In only exceptional cases does the antibiotic seem significant in this regard. None of our patients were treated prior to their fatal illness with any significant amount of antibiotics. It is true that after they became ill various types of antibiotics were used in profusion, but none had any significant effect in altering the expected course of the illness.

The role that corticotropin and cortisone play in influencing the reaction of the host to infection is becoming well established. The present status of our knowledge of the effect of these drugs on various types of infection has been summarized by Schwartzman [41] in a Symposium of the Section of Microbiology of the New York Academy of Medicine in 1953. The adverse effect of these drugs on infection with tubercle bacillus and pneumococci and on influenza, malaria, syphilis, and even poliomyelitis, is described. He comments that it is increasingly apparent that these hormones may alter the clinical response to infectious agents and change or obliterate many of the usual clinical

manifestations of the infection. Organisms which are not usually fatal for certain hosts may become rapidly invasive and produce fatalities when the host animal is receiving one of these hormones. The effect of cortisone on the infectivity of mice with C. immitis has been shown to be detrimental in early phases of the host's response, as determined by histologic examination of tissues (Newcomer and associates [42]). There are a few scattered reports of the possibility of adverse effects of hormonal therapy on various mycoses (Lauzé [43]). He reported a case of fatal C. neoformans septicemia with a localized focus at the base of one lung developing in a young woman during the course of extended cortisone and antibiotic therapy for pigmented cirrhosis of the liver and cardiac insufficiency, with intercurrent infections and episodes of failure. The author discusses both types of therapy but points out that cryptococcosis is a rare endogenous type of infection, not reported as arising during treatment with antibiotics alone. Leo, Levin, Rivo, and Barrett,[44] in an addendum to a paper discussing the development of active tuberculosis during therapy with corticotropin and cortisone for unrelated conditions, mention a fatal case of acute, disseminated actinomycosis, established at autopsy as a complication of treatment of acute lymphatic leukemia.

Newcomer and associates [42] recently summarized the scant clinical literature on known mycotic infections treated experimentally with corticotropin or cortisone. These included one case of disseminated coccidioidomycosis, which terminated fatally with no apparent alteration in the clinical picture, and three cases of blastomycosis, two of which also had systemic involvement. All three cases consistently manifested increased inflammation and exudation at the site of the skin lesions, and the authors concluded that this form of therapy was definitely not indicated in this disease.

Of our five patients, there were two who received corticotropin and cortisone for prolonged periods—one patient developed cryptococcosis and the other a dual infection of systemic moniliasis and aspergillosis with multiple Aspergillus abscesses in the brain. The other two cases of cryptococcosis and the one of coccidioidomycosis did not receive these hormones. It is impossible to draw any conclusion, but there is room for speculation as to whether corticotropin and cortisone played any role in predisposing them to a virulent fungus infection or whether both these patients, who were chronically ill for some time, had lost resistance to these organisms for some unrelated reason. Of those who had hormones, Case 1 had Hodgkin's sarcoma for a long time and was also chronically ill. In Case 3 the infection followed a head injury, which may be significant, and Case 4 had coccidioidomycosis, which is endemic. Whether corticotropin and cortisone are causally related to the pathogenic behavior of the organism may not be clear, but most assuredly it does nothing to prevent it, and in the present state of our knowledge their use in such cases is conflictual. On the other hand, one must not lose sight of the fact that cortisone is of value in the face of overwhelming infection because of its toxemia-inhibiting properties and, of necessity, must be utilized.

SUMMARY

It is apparent that the clinician remains powerless in most instances in the management of fungus infections. The authors encountered a splendid opportunity over a period of one year to treat five cases, including three of cryptococcosis, one of coccidioidomycosis, and one of aspergillosis. Treatment included symptomatic and supportive care, blood transfusions, the sulfonamide drugs, penicillin, chlortetracydine (Aureomycin), dihydrostreptomycin, polymyxin B, autogenous vaccines of the cryptococci, potassium iodide, methylrosaniline chloride (gentian violet), 2-aminostilbamidine, corticotropin, and cortisone. Repeated spinal punctures were made to relieve intraspinal pressure. A new antibiotic cycloheximide (Actidione) was used in every case of cryptococcosis, and it was our conclusion that

this drug was of no benefit and that in one case it appeared to hasten the patient's death by the development of bilateral encephalomalacia.

It is hoped that with the recent surge of interest in the areas of medical mycology newer and more formidable agents will appear, not only as therapy for the alleviation of symptoms but also as means for ultimate recovery.

Actidione was furnished through the courtesy of The Upjohn Company, Kalamazoo, Mich.

REFERENCES

1. Nickerson, W. J.: Medical Mycology, Ann. Rev. Microbiol. **7**:245, 1953.

2. Smith, D. T.: Fungus Infections in the United States, J. A. M. A. **141**:1223, 1949.

3. Zimmerman, L. E.: Fatal Fungus Infections Complicating Other Diseases, J. Clin. Path. **25**:46, 1955.

4. Zenker, F. A.: Encephalitis mit Pilzentwickelungem Gehirn, Jahresb. Gesellsch. Natur-Heilk. Dresden **62**:51, 1861.

5. Sahs, A. L.: Meningitis, in Clinical Neurology, A. B. Baker, Editor, New York, Paul B. Hoeber, Inc., 1955, Vol. 1, pp. 613-667.

6. Freeman, W.: Fungus Infections of the Central Nervous System, Ann. Int. Med. **6**:595, 1932.

7. Alajouanine, T.; Houdart, R., and Drouhet, E.: Surgical Spinal Forms of Torulosis: Toruloma of Cauda Equina, Rev. neurol. **88**:153, 1953.

8. Hyslop, G. H.; Neal, J. B.; Kraus, W. M., and Hillman, O. A.: A Case of Sporotrichosis Meningitis, Am. J. M. Sc. **172**:726, 1926.

9. Wolf, A.; Benham, R., and Mount, L.: Maduromycotic Meningitis, J. Neuropath. & Exper. Neurol. **7**:112, 1948.

10. Kurrein, F.: Cerebral Mucormycosis, J. Clin. Path. **7**:141, 1954.

11. Globus, J. H.; Gang, K. M., and Bergman, P. S.: Torula Meningoencephalitis, J. Neuropath. & Exper. Neurol. **10**:208, 1951.

12. Carton, C. A.: Treatment of Central Nervous System Cryptococcosis: A Review and Report of 4 Cases Treated with Actidione, Ann. Int. Med. **37**:123, 1952.

13. Kligman, A. M., and Mescon, H.: The Periodic-Acid-Schiff Stain for the Demonstration of Fungi in Animal Tissues, J. Bact. **60**:415, 1950.

14. Mosberg, W. H., Jr., and Arnold, J. G., Jr.: Torulosis of the Central Nervous System: Review of Literature and Report of 5 Cases, Ann. Int. Med. **32**:1153, 1950.

15. Gendel, B. R.; Ende, M., and Norman, S. L.: Cryptococcosis: A Review with Special Reference to Apparent Association with Hodgkin's Disease, Am. J. Med. **9**:343, 1950.

16. Rodger, R. C.; Terry, L. L., and Binford, C. H.: Histoplasmosis, Cryptococcosis, and Tuberculosis Complicating Hodgkin's Disease: Report of a Case, Am. J. Clin. Path. **21**:153, 1951.

17. Collins, V. P.; Gellhorn, A., and Trimble, J. R.: Coincidence of Cryptococcosis and Diseases of the Reticulo-Endothelial and Lymphatic Systems, Cancer **4**:883, 1951.

18. Zimmerman, L. E., and Rappaport, H.: Occurrence of Cryptococcosis in Patients with Malignant Diseases of the Reticuloendothelial System, Am. J. Clin. Path. **24**:1050, 1954.

19. Wilson, N. M., and Duryea, G. W.: Cryptococcus Meningitis (Torulosis) Treated with a New Antibiotic, Actidione, A. M. A. Arch. Neurol. & Psychiat. **66**:470, 1951.

20. Martin, H., and Podberg, F.: Torulosis of the Brain, Arch. Neurol. & Psychiat. **62**:679, 1949.

21. Ley, A.; Jacas, R., and Oliveras, C.: Torula Granuloma of Cervical Spinal Cord, J. Neurosurg. **8**:327, 1951.

22. Weidman, F. D., and Freeman, W.: India Ink in the Microscopic Study of Yeast Cells, J. A. M. A. **83**:1163, 1924.

23. Smith, D. T.: Fungus Infections in the United States, J. A. M. A. **141**:1223, 1949.

24. Haspel, R.; Baker, J., and Moore, M. B., Jr.: Disseminated Cryptococcus Neoformans, New Orleans M. & S. J. **101**:573, 1949.

25. Kligman, A. M., and Weidman, F. D.: Experimental Studies in the Treatment of Human Torulosis, Arch. Dermat. & Syph. **60**:726, 1949.

26. Forbus, W. D.: Coccidioidomycosis: Study of 95 Cases of Disseminated Type with Special Reference to Pathogenesis of the Disease, Mil. Surgeon **99**:653, 1946.

27. Schlumberger, H. G.: A Fatal Case of Cerebral Coccidioidomycosis with Culture Studies, Am. J. M. Sc. **209**:843, 1945.

28. Abbott, K. M., and Cutler, O. I.: Chronic Coccidioidal Meningitis, Arch Path. **21**:320, 1936.

29. Jenkins, V. E., and Postlewaite, J. C.: Coccidioidal Meningitis: Report of 4 Cases, with Necropsy Findings in 3 Cases, Ann. Int. Med. **35**:1084, 1951.

30. Rand, C. W.: Coccidioidal Granuloma: Report of 2 Cases Simulating Tumor of the Spinal Cord, Arch. Neurol. & Psychiat. **23**:502, 1930.

31. Norman, D. D., and Miller, Z. R.: Coccidioidomycosis of the Central Nervous System: A Case of 10 Years' Duration, Neurology **4**:713, 1954.

32. Christison, I. B., and Conant, N. F.: Antifungal Activities of Some Aromatic Diamadines, J. Lab. & Clin. Med. **42**:638, 1953.

33. Egas Moniz, and Loff, R.: Aspergillose cérébrale, Presse méd. **39**:273, 1931.

34. Iyer, S.; Dodge, P. R., and Adams, R. D.: Two Cases of Aspergillus Infection of the Central Nervous System, Neurol. Neurosurg. & Psychiat. **15**:152, 1952.

35. Zimmerman, L. E.: Candida and Aspergillus Endocarditis, Arch. Path. **50**:591, 1950.

36. Woods, J. W.; Manning, I. H., Jr., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207, 1951.

37. Kunstadter, R. H.; MacLean, H., and Greengard, J.: Mycotic Endocarditis Due to Candida Albicans, J. A. M. A. **149**:829, 1952.

38. Hutchison, M. K.: Moniliasis: A Complication of Antibiotic Therapy, J. Kansas M. Soc. **54**:436, 1953.

39. Reiches, A. J.: Antibiotic Sensitivity and Moniliasis, A. M. A. Arch. Dermat. & Syph. **64**:604, 1951.

40. Kligman, A. M.: Are Fungous Infections Increasing as a Result of Antibiotic Therapy? J. A. M. A. **149**:979, 1952.

41. Schwartzman, G., Editor: Symposium of the Section of Microbiology of the New York Academy of Medicine in 1953, New York, Columbia University Press, 1953.

42. Newcomer, V. D.; Wright, E. T.; Tarbet, J. E.; Winer, L. H., and Sternberg, T. H.: The Effects of Cortisone on Experimental Coccidioidomycosis, J. Invest. Dermat. **20**:315, 1953.

43. Lauzé, S.: Torula Infection in a Patient Treated with Antibiotics and Cortisone, Union méd. Canada **81**:935, 1952.

44. Leo, F.; Levin, M. H.; Rivo, J. B., and Barrett, T. F.: Development of Active Pulmonary Tuberculosis During ACTH and Cortisone Therapy, J A. M. A. **147**:242, 1951.

CORRECTION

In the article "Irregular Fluctuation of Elevated Cerebrospinal Fluid Pressure" by Arthur Ecker, in the December, 1955, issue of the ARCHIVES, page 641, a phrase was omitted from the subtitle. The subtitle should read as follows: "Such Fluctuations as a Measure of Dysfunction of Cerebral Blood Vessels in Cerebrosvascular Episodes, Pseudotumor Cerebri, and Head Injury."

Pentylenetetrazol (Metrazol) Activation of the Electroencephalogram

CAPT. HALBERT H. SCHWAMB, (MC)
LIEUT. COL. ROY E. CLAUSEN Jr. (MC)
and
LIEUT. COL. JOHN W. SUMNER Jr. (MC),
U. S. Army

The purpose of this study is to evaluate one of the methods of pentylenetetrazol (Metrazol) activation of the EEG in clinical and control groups in order to gain further information regarding the validity of such a procedure as an adjunct to the diagnosis of seizure states. A comparison is made between pentylenetetrazol activation and sleep and hyperventilation procedures in the same clinical group.

METHODS

A. The Control Group.—This group consisted of 30 men ranging in age from 18 to 43 years, with a median age of 21 years, 14 subjects being 20 and 21 years of age, and only 2 being 18 years of age. Clinical history was obtained on all controls and revealed no evidence of episodes of dizziness, unconsciousness and/or convulsions, sudden head pain, numbness, abdominal pain, past encephalitic-like disease, or family history of seizure state. Twenty-four subjects had no history of head injury, and six had a history of a head injury producing unconsciousness of only a few minutes' duration in the distant past. These were all voluntary controls who were on active military duty and were not hospital patients, except two who were hospitalized for peripheral nerve disease. Routine awake, three-minute hyperventilation, and pentylenetetrazol-activated EEG records were obtained in the controls.

B. The Clinical Group.—This group consisted of 185 patients ranging in age from 12 to 48, with a median age of 22 years. The greatest number were between 20 and 22 years, and only four patients were under 18. The clinical group was subdivided on the basis of clinical history and examination and not on the basis of the EEG. The first group was termed proved and probable idiopathic seizure states on the basis of highly suggestive clinical history, seizures witnessed by medical personnel, and adequate inpatient evaluation, including the use of hypnosis or amobarbital (Amytal) interview techniques to test ictal amnesia as recommended by Sumner and co-workers.[9] This group was subdivided in turn on the basis of seizure type into grand mal, petit mal, psychomotor, and mixed types. An organic group consisted of patients with demonstrated central-nervous-system disease and was subdivided into those with probable or proved seizures and those without seizures. A third group was termed functional and was divided into patients with "blackouts" or "syncope" and those without such symptoms. The bulk of the functional group consisted of patients with tension headaches, "dizzy spells," with or without actual "blackouts," and psychiatric conditions in which the EEG was obtained for clearance purposes. A migraine group consisted of only seven patients in whom the diagnosis was made on the basis of hemicrania, visual scotoma, associated gastrointestinal upset, and in most cases a family history of similar disorder. A no-disease group consisted of prisoner cases and other individuals receiving routine clearance examinations.

An eight-channel Grass Console Model No. III-A, 1948, using frontal, parietal, anterior temporal, temporal, and occipital unipolar leads was used. All patients in the clinical group had awake records, followed by three minutes of hyperventilation, sleep, and then pentylenetetrazol activation.

Awake records were considered normal if they showed symmetrical alpha or low-voltage fast activity, allowing random 5 to 7 cps slow activity of a voltage less than that of the prevailing alpha rhythm and to an extent not more than 10% of the entire record. Borderline awake tracings fell generally into the S_1 and F_1 classifications of Gibbs and co-workers.[4] Abnormal awake records included those in which large amounts of irregular slow, paroxysmal, or focal activity of any type occurred. Three minutes of hyperventilation was given each

Submitted for publication Dec. 28, 1955.

From the Department of Neuropsychiatry, Neurology Service, Fitzsimons Army Hospital, Denver.

Mr. Ian McPhee, Chief Technician, EEG Laboratory, Fitzsimons Army Hospital, gave technical assistance in this study.

patient. Build-up was not considered significant unless the change in the basic pattern persisted for more than one minute after hyperventilation terminated or was paroxysmal or focal in nature.

In most instances sleep was induced by 1½ to 3 grains (0.1 to 0.2 gm.) of secobarbital (Seconal) orally, the higher dose being given only when the lower failed to produce a satisfactory level of sleep. During sleep special interest was placed in the occurrence of 6- to 14-per-second positive spikes or focal negative spikes as described by Gibbs and co-workers.*

Following these studies 10 cc. of a 5% solution of pentylenetetrazol was given intravenously at the rate of 0.5 cc. every 30 seconds, a method used by Merlis and co-workers,† and approximating the "slow" method of Cure and co-workers.[2] The administration of pentylenetetrazol was usually stopped when paroxysmal activity occurred, otherwise the total amount of 500 mg. was given. EEG changes produced by pentylenetetrazol were of three types: "slow activity," the occurrence of bursts of 4- to 7-per-second generalized slowing of high voltage; "paroxysmal activity," generalized spikes or spike-wave formation of 2 to 6 per second, and "focal activity" of spikes or slow waves.

RESULTS

This study attempts to determine the median amount of pentylenetetrazol necessary to produce slow, paroxysmal, or focal activity in the EEG pattern of clinical and control groups, as well as the percentages of the groups showing such "activation." In addition the EEG was observed for persistence of all types of activity produced following the termination of the pentylenetetrazol injection.

A. The Control Group.—This group is reported in detail regarding pentylenetetrazol response. Of 30 controls, 7, or 23%, showed slow activity at a median dose of 200 mg. Persistence of such activity followed the injection of pentylenetetrazol in 43% of those showing the slow response. Twelve of the thirty controls, or 40%, showed a paroxysmal response at a median dose of 325 mg. Persistence occurred in 50% of those showing such a response, and a grand mal seizure occurred in one. Sixteen per cent of the controls showed a paroxysmal response by 250 mg., twenty per cent by 300 mg., thirty-seven per cent by 450 mg., and forty per cent by 500 mg. Sixteen per cent showed a slow response by 250 mg., twenty per cent by 400 mg., and twenty-three per cent by 450 mg. Two of the twelve controls showing paroxysmal response had frank 3-per-second spike and slow wave generalized "petit mal" discharges; one was followed by a grand mal seizure. Twenty-seven controls had normal awake and hyperventilation records prior to pentylenetetrazol activation. Three had borderline awake records, and one of these had a mild build-up during hyperventilation. The control who had a clinical grand mal seizure at 375 mg. had a normal awake and hyperventilation record before pentylenetetrazol. Four of the six controls giving a history of very minor head injury had no pentylenetetrazol activation of any type, one other showed a slow response at 250 mg. without persistence, and the other a slow response at 200 mg. which persisted.

The percentage of controls showing paroxysmal response in this series is higher than in the group reported by Cure and co-workers[2] or by Merlis and co-workers.[7] It is also higher than the group reported by V. Fuglsang-Frederiksen,[3] who used a more rapid method of pentylenetetrazol administration. The paroxysmal response percentage in controls is similar to the group reported by Cohn and co-workers,[1] who found 47%, or 7, of 15 controls to show "spike-dome" activity. They gave pentylenetetrazol at 100 mg. per minute to the point of EEG activation or for a total of 300 mg. The mean pentylenetetrazol dose producing a paroxysmal response in the control group, 325 mg., compares with the "minimum threshold EEG" of 340 mg. for nonepileptics reported by Ziskind and Bercel.[10]

B. The Clinical Group.—Results in the clinical group are noted in Table 1. It should be recognized that some of the subgroups are too small to draw definite correlations. Twice as many of the idiopathic seizure group showed a slow response as did controls; however, the median pentylenetetrazol dose was higher and persistence was less

* References 5 and 6.

† References 7 and 8.

TABLE 1.—*Results in the Clinical Group*

	No.	Pentylenetetrazol, Median Dose, Mg.	Slow Response		Persistence of Slow Response		Pentylenetetrazol, Median Dose, Mg.	Paroxysmal Response		Persistence of Paroxysmal Response	
			No.	%	No.	%		No.	%	No.	%
Control groups	30	200	7	23	3	43	325	12	40	6	50*
Proved and probable idiopathic seizure states by type											
Grand mal	17	250	10	58	3	30	300	13	76	10	79†
Petit mal	10	100	3	30	1	33	325	8	80	6	66
Psychomotor	4	0	0	0	0	0	350	3	75	0	0
Mixed	9	275	6	66	1	16	325	3	33	1	33
Total idiopathic seizure states	40	225	19	48	5	26	325	27	68	17	63
Organic with proved or probable seizures											
Grand mal	6	125	1	17	1	100	300	1	17	1	100*
Petit mal	1	450	1	100	0	0	500	1	100	1	100
Psychomotor	2	200	2	100	0	0	200	1	50	1	100
Mixed	3	250	2	66	0	0	0	0	0	0	0
Jacksonian	5	0	0	0	0	0	275	2	40	0	0
Total organic with seizures	17	250	6	35	1	16	300	5	29	3	60
Organic without seizures											
Trauma	11	175	2	18	1	50	175	4	36	4	100*
Multiple sclerosis	4	275	2	50	1	50	200	1	25	1	100
Miscellaneous	9	475	1	11	0	0	350	2	22	0	0
Total organic without seizures	24	300	5	21	2	40	250	7	29	5	71
Functional group											
With "blackouts"	44	225	9	43	5	26	325	19	43	10	53
Without "blackouts"	36	200	11	31	4	36	300	8	22	3	38
Total functional	80	225	30	38	9	30	325	27	34	13	48
Migraine	7	350	5	71	0	0	400	1	14	0	0
No disease	17	300	3	19	1	33	325	4	24	2	50

* 1 grand mal seizure.
† 2 grand mal seizures.

in the seizure group. Twenty-eight per cent more of the idiopathic seizure group than controls showed paroxysmal activity; however, the median pentylenetetrazol dose was the same, and persistence was only 13 per cent more in the seizure group. In the idiopathic seizure subgroups patients with clinical grand mal, petit mal, and mixed type seizures showed greater percentages with slow response than controls; however, the median dose was only less in petit mal, 100 mg. as opposed to 200 mg. for controls. Persistence of the slow response was less in all the subgroups than in the controls. None of the psychomotor subgroup showed a slow response. Grand mal, petit mal, and psychomotor cases all showed a higher percentage of paroxysmal response than the controls. The greatest difference was in petit mal, 80%, as opposed to 40% for controls. There was no significant difference in the median dose level required for activation of the idiopathic seizure group and the control group. Persistence of paroxysmal response was greater than in controls only in the grand mal and petit mal subgroups by 29% and 16%, respectively. Twice as many of the petit mal subgroup showed a paroxysmal response as controls; however, the median dose was the same and the tendency to persist was only slightly greater in petit mal cases. Of the organic group with seizures, 12% more showed a slow response than controls. The median dose was higher and there was less tendency for persistence in the organic group. Paroxysmal activity occurred 11% less frequently in the organic group with seizures. The median dose was slightly lower in the organic group, and paroxysmal activity persisted in 10% more than in the controls. None of the patients having clinical Jacksonian seizures had focal abnormalities brought out by pentylenetetrazol activation.

It is of interest that the percentage of paroxysmal response was the same in the organic group without seizures as in the organic group with seizures. The median dose was actually 50 mg. lower in the group without seizures than in those with seizures, and a slightly greater tendency for persistence of the paroxysmal response occurred in the group without seizures.

Fifteen per cent more of the total functional group showed a slow response; however, the median dose was higher and the persistence of slow activity was less than in controls. Regarding paroxysmal response, the total functional and control groups were almost identical in all respects. In the functional group with blackouts, a group in which an activation procedure might be of great help in the differential diagnosis of a possible seizure state, 20% more showed a slow response than the controls; however, the median dosage was higher and the persistence of the slow response was less in this group than in the controls. Paroxysmal activation in the functional group with blackouts was almost identical in all respects with the results obtained in the control group. Twenty-one per cent more of the patients classified clinically as functional with "blackouts" showed a paroxysmal response, and nineteen per cent more showed persistence of such response, but the median dose for such response was higher than in the group classified as functional without "blackouts."

A comparison of the total functional group with the idiopathic seizure group showed no significant difference in percentages showing a slow response or in median dose and persistence of such a response. Twice as many of the idiopathic seizure group showed a paroxysmal response as the functional group. The median dose was exactly the same, and 15% more showed persistence of paroxysmal activity. A comparison of slow response in the functional group with "blackouts" and the idiopathic seizure group showed results to be almost identical in all respects. Paroxysmal activity occurred in 25% more of the idiopathic seizure group; however, the median dose was the same, and 10% more of the group showed persistence of the paroxysmal response than was noted in the functional group with "blackouts."

In comparing a total nonseizure group, including controls, no-disease functional, and migraine groups with the total seizure-state cases, that is, organic with seizures and the idiopathic seizure states, 10% more of the seizure-state group showed a slow response. The median dose was the same, and 5% fewer of the seizure-state group showed persistence. Twenty-three per cent more of the seizure group showed a paroxysmal response. The median dose was the same, and 20% more of the seizure group showed persistence.

Frankly abnormal awake records were noted in 1.5% of a nonseizure group consisting of controls, functional, no-disease, and migraine cases and in 10.5% of the total seizure-state group. Of the total functional, no-disease, and migraine groups, 8.6% showed hyperventilation response, as compared with 21% of the total seizure-state group. Of the no-disease, functional, and migraine groups, 8.6% showed an abnormal

TABLE 2.—*Comparison of Control and Clinical Groups with Respect to Abnormal Activity During Awake Records, Hyperventilation, and Sleep*

	Total No.	Abnormal Awake EEG		Abnormal Sleep EEG		Abnormal HV EEG Response	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Controls	30	0	0	Not done		2	7
Proved and probable idiopathic seizure states	40	4	10	7	18	11	28
Organic with proved and probable seizures	17	2	12	5	29	1	6
Organic without seizures	24	2	8	3	13	0	0
Functional	80	2	3	7	9	8	10
Migraine	7	0	0	1	14	1	14
No disease	17	0	0	1	6	0	0

sleep response, as compared with 21% of the total seizure-state group. These compilations are made from the data in Table 2. These results should be compared with pentylenetetrazol activation in which a slow response occurred in 34% of the nonseizure group, including controls, functional, no-disease, and migraine, and in 44% of the total seizure-state group. A paroxysmal response to pentylenetetrazol was noted in 33% of the total nonseizure group and in 56% of the total seizure group.

CONCLUSIONS

1. Although pentylenetetrazol activation of a paroxysmal response in the EEG occurs in a higher percentage of patients with probable or proved seizures than in a control group or in nonseizure clinical groups, the difference between such groups does not indicate that this activation procedure differentiates them with sufficient reliability.

2. A slow response in the 4 to 7 cps range occurs in the EEG in general with smaller amounts of pentylenetetrazole. A study of the slow response does not offer consistent clinical correlations and therefore is of no diagnostic value.

3. Differences in median doses of pentylenetetrazol, producing either slow or paroxysmal response, between clinical and control groups were not significant.

4. Persistence of paroxysmal activity is higher in the idiopathic seizure group than in the control or no-disease groups, but not sufficiently to be of definite clinical value.

5. Activation by hyperventilation and sleep in the total seizure group was nearly three times as high as in a total nonseizure group, giving a relatively higher degree of correlation than is obtained by pentylenetatrazol activation. However, activation by hyperventilation and sleep was disappointing, as only 21% of the total seizure group was activated by hyperventilation and 21% by the sleep method.

6. In the military setting it is recognized that the average group of patients who are presented for study to determine the presence or absence of a seizure state are afflicted less severely than a comparable group in the civilian population, since a great majority of those suffering from a severe seizure state will of necessity not be inducted or enlisted into military service. Nevertheless, it is precisely in the former group that activation procedures should have their greatest clinical value. From this study it would appear that none of the activation methods used offered a sufficient degree of reliability to differentiate adequately the groups concerned.

REFERENCES

1. Cohn, R.; Nardini, J. E., and Boswell, W. H.: A Comparison of Provocative Agents in the Epilepsies and in Controls, Neurology **2**:481, 1952.

2. Cure, C.; Rasmussen, T., and Jasper, H. H.: Activation of Seizures and Electroencephalographic Disturbances in Epiletic and in Control Subjects with "Metrazol," Arch. Neurol. & Psychiat. **59**: 691, 1948.

3. Fuglsang-Frederiksen, V.: Activation of EEG Disturbances with Metrazol (Pentazol) in Epileptics, Normals and Patients with Syncopal Attacks, Electroencephalog. & Clin. Neurophysiol. **4**:471, 1952.

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Patients, Arch. Neurol. & Psychiat. **50**:111, 1943.

5. Gibbs, E. L., and Gibbs, F. A.: Diagnostic and Localizing Value of Electroencephalographic Studies in Sleep, A. Res. Nerv. & Ment. Dis., Proc. **26**:366, 1947.

6. Gibbs, E. L., and Gibbs, F. A.: Electroencephalographic Evidence of Thalamic and Hypothalamic Epilepsy, Neurology **1**:136, 1951.

7. Merlis, J. K.; Henriksen, G. F., and Grossman, C.: Metrazol Activation of Seizure Discharges in Epileptics with Normal Routine Electroencephalograms, Electroencephalog. & Clin. Neurophysiol. **2**:17, 1950.

8. Merlis, J. K.; Grossman, C., and Henriksen, G. F.: Comparative Effectiveness of Sleep and Metrazol-Activated Electroencephalography, Electroencephalog. & Clin. Neurophysiol. **3**:71, 1951.

9. Sumner, J. W., Jr.; Cameron, R. R., and Peterson, D. B.: Hypnosis in Differentiation of Epileptic from Convulsive-like Seizures, Neurology **2**:395, 1952.

10. Ziskind, E., and Bercel, N. A.: Preconvulsive Paroxysmal Electroencephalographic Changes After Metrazol Injection, J. Nerv. & Ment. Dis. **111**:52, 1950.

Special Articles

THE CUTANEOUS SENSORY MODALITIES

A Critique of Their "Specificity"

FRANCIS SCHILLER, M.D., San Francisco

ALTHOUGH Aristotle's enumeration of man's five special senses is no longer accepted without reservations and additions, most authorities deviate only little from that classical and popular account. Likewise, students are taught some version of Johannes Müller's theory of specific nerve energies. Thus it is widely believed that, whatever the effective stimulus, a certain anatomically distinct sense organ will transmit to consciousness none but its own sensory quality.

The axiom of specificity is carried over to sensations other than vision, hearing, smell, and taste. By "other" we must understand all those superficial and deep sensations which have their receptors diffusely scattered throughout the body and over its surface, with the exception of the vestibular organ, which is discrete. The welter of experience derived from these "other" sense organs has always made it difficult to find their common denominator, on the one hand, and their individual status, on the other. There was hope that this awkward fifth sense of "feeling" would yield to ultimate analysis when, about 70 years ago, various independent investigators discovered the "sensory spots" in the skin and endowed these with anatomical and functional discreteness.

Until recently the four somesthetic modalities—touch, heat, cold, and pain—have formed an unquestioned basis for investigations in the laboratory and clinic. As the general argument runs, a fixed and specific structural chain, from the receptor to its representation in the cortex, must invariably be responsible for what we call "hot," "touch," "painful prick," no less than there are specific conveyers for what we call "blue," a "high-pitched sound," or "bitter."

The objections which such reasoning encounters are considerable, not only on physical but on anatomical, physiological, psychological, and semantic grounds; it might be worth assembling them here. An attempt will be made to follow the argument about specificity through its customary stages or "levels." Such an analysis seems to open possibilities for a revised hypothesis of our "fifth sense."

Received for publication June 8, 1955.

From the Biomechanics Group and the Department of Neurology, University of California School of Medicine.

PHYSICAL STIMULI

The relevance of the type of environmental stimulus for perception has been minimized even by the adherents of specificity, because any particular nerve and its endings can be excited by several forms of energy. By the same token, one form of energy can stimulate various types of sensory organs; e. g., radiant energy affects the retina as well as the skin, vibratory energy the ear as well as the deep tissues, thermal energy, the heat, pain, and vestibular endings, and so forth. "Adequacy" of stimuli is thus capable of a fairly broad interpretation. The effectiveness of a stimulus has its limitations, however; it is limited not only by its intensity but by its wave length, its duration, and its rate of increment, gradient, or background. Physics, originally concerned with material gathered from sense data, has increasingly endeavored to supplement, if not eliminate, the senses as instruments of observation. Not only are sense organs relatively unreliable, lacking in discrimination, and unstable; they may even be overdiscriminating and report changes in quality where the physicist's evidence points to a mere change in intensity, as in the case of thermal changes producing sensations of cold, warmth, and pain, or mechanical energy producing sensations of touch, pressure, proprioception, and pain. If, indeed, the physicist in his own field still distinguishes various kinds of energies, these are no longer determined by immediate sensory experience, and the kinds of energies defined by textbooks of physics have only a very superficial equivalent in perception.

This is nowhere truer than in the case of pain. Putting aside the all-pervading problem of subjectivity and social conventions, such as language, pain-producing stimuli are, in terms of physics, the least specific of all, representing nothing more than "a turn of the screw" in the application of any kind of physical energy. In the realm of touch or pressure, for instance, we can start from a mechanical stimulus value which is below the sensory threshold and go on to one above threshold, and still remain within the same kind of tactile experience. Painful stimuli, on the other hand, are in fact pressure and temperature stimuli: there is nothing physically specific in the threshold stimulus for pain; no change in the kind of stimulus is required to produce a change in the kind of experience. Mere variations in stimulus frequency, known to produce qualitative changes in the perception of color or pitch, do not bring about a conversion from touch to pain: only a change in intensity will do this.

The nervous organization is thus an imperfect mirror of physical properties, and stimuli alone are, in turn, no gauge of nervous activity and sensory experience. (Only an out-and-out solipsist would claim that physical energies follow the pattern of nervous organization!)

SENSORY SPOTS AND NERVE ENDINGS

Blix,[1] Goldscheider,[2] Donaldson,[3] and von Frey[4] found that one relatively small area of the skin was responsive to one, but refractory to another, form of stimulation, while another area responded differentially. It seemed evident that with regard to sensation the skin was a mosaic composed of three or four types of spots and that each type was specifically tuned to mediate between one basic physical energy and one basic sensory experience. It is not generally appreciated how cautious these original observers were in stating their generalizations. Nevertheless, the next step, to establish close correlation between one type of macroscopic sensory spot and one type of underlying, characteristically shaped microscopic nerve

ending, promised to be simply a matter of diligent study. But, leaving aside the morphological problem of specific nerve endings, the discrepancy between their minute size and the much larger size of the stimulated areas made any such correlation dubious, as did the frequent overlap and inconstancy of the spots, both in the same subject and in different subjects.* For instance, "paradoxical warmth" from "warm spots" when stimulated with a low temperature, and "paradoxical cold" under the reverse conditions, were found only in 27 out of 9000 stimulations by Jenkins.[7] If specificity of spots were valid, paradoxical sensation should be the rule and not have an incidence of 0.3%. On the other hand, if there are "paradoxical" spots, they cannot be called specific, unless one postulates a specific paradoxical nerve energy.

More, and better controlled, experimental procedures discredited the work on spots. Replacing them, Tower's [8] concept of a "unit for sensory reception" was based on single-fiber electroneurograms. It only confirmed the theory of Sfameni † and Ruffini,[9] to the effect that (*a*) one nerve fiber is distributed over a considerable macroscopic territory and (*b*) one macroscopic spot is innervated by the branches and endings of more than one fiber. In other words, the peripheral nervous arrangement does not, in the relation of one to one, reflect the punctate nature of stimuli and areas stimulated.

This is at least true of the cornea, a part of the body surface supplied only by the free endings of unmyelinated nerve fibers. Claims that the latter fact supported the specificity of naked fibers for the conduction of pain were disproved by the observation that in the cornea touch and pressure are apprehended as well as pain.‡ The orbicularis oculi reflex, elicited by a cotton wisp applied to the cornea, is accompanied by some discomfort, but not necessarily by the sort of pain that is felt when a foreign body is lodged on the eye.

The fallacy of specific sensory spots became even more evident as support vanished for the belief that specific sensory endings subserve the four modalities of the skin. Nearly 100 years ago Schiff [13] had already pointed out that Meissner claimed no special function for the corpuscles which he described, and added that "they do not serve in tactile experience, for we feel touch with areas of skin where there are none present. . . . No nerve by itself can do such a thing." Ruffini [9] taught that the various eponymous end-organs are but variations and modifications of one another, protean and of all sizes, and that no single ending belongs to one unmistakable morphological class. There are more forms than a tetrad of modalities indicates. Thus, "when the morphologist begins to . . . attribute such and such a sensation to such and such a nerve expansion, and when he finally takes it upon himself to lay down the law for functional modalities, he is simply building a house of cards." According to Stöhr's [14] equally comprehensive and scholarly review, the shape of an ending seems to play but an indifferent part in function; the diversity of forms is infinitely great; Meissner's, Paccini's, and Ruffini's corpuscles are arbitrary types isolated from an endless, continuous line of varieties—not fixed, separate, and invariable, but a vast array of modifications shading off into one another. All types of endings are found in surfaces reputedly endowed with less than four "modalities"—such as the oral mucosa (high pain threshold) and the glans penis (only pain and cold sensations). Formed endings, with and

* References 5 and 6.

† Sfameni, 1904, cited by Ruffini.[9]

‡ References 10 to 12.

without encapsulation, are demonstrable in the plexus chorioideus, the pericardium, etc. Sinclair and associates [15] have shown that at the back of the human auricle skin can be adequately sensitive to any conventional type of stimulus, yet possesses only free endings and none of the specialized end-organs. More recent work from the same school [16] confirms Schiff's, Ruffini's, and Stöhr's work denying specificity to sensory nerve endings.

In the teeth a nerve plexus has been described for the pulp (Stöhr [14])—free endings in the dentin; terminal reticular and only "small end-rings close to the bony alveoles" in the periodontal membrane (Sprenkel [17]). But in health our teeth feel sensations other than pain, such as touch, vibration, heat, and cold.

The innumerable possibilities in which nerve endings may be branched, coiled, looped, and encapsulated have been compressed into the set types with which the textbooks present us. But their actual variety is too great, and their individual definition too poor, to allow a one-to-one relationship between sensory endings and a tetrad of modalities.

NERVE FIBERS

The work of Erlanger and Gasser seemed to confirm the long-sought-for existence of special nerve fibers for the conduction of various sensations. This work attributed fast conduction to large, and slow conduction to small, fibers. But Gasser § explicitly stated that "fibers conducting different modalities of sensation are widely distributed throughout the various fiber sizes," and "there seems to be little possibility of associating any one sensation with an elevation in the electroneurogram." Fiber size is a statistical concept.[20] A maximum incidence within a certain range characterizes one group, but the margins between groups or averages cannot be drawn sharply. An analysis of the fiber spectrum, therefore, could not be expected to yield four discrete modalities of nerve conduction according to fiber size.

Nevertheless, the delayed, or second, pain which follows a prick or burn seemed to fit the properties of thin and unmyelinated C-fibers, with their delayed elevation in the electroneurogram. Moreover, cocaine, which abolishes conduction in these fibers before it does so in the large, myelinated A-fibers, also abolishes pain before rendering the skin completely anesthetic. On the contrary, oxygen deprivation, which abolishes conduction first in A-, then in C-fibers, abolishes all other sensations before that of pain. The two agents, however, have the same effect among the subgroups within the range of A-fibers, as on the oscilloscope they abolish their relatively smallest component, the delta elevation, first.

Sinclair and Hinshaw ‖ made comparative studies of nerve blocks produced by procaine, compression, and cooling. The order of disappearance of the four modalities varied with the procedure used. But with any one blocking agent, the order of sensory failure was by no means invariable, although there existed a statistically valid regularity of disappearance, especially in the case of anesthesia by way of cooling. Not only were there individual variations; deliberate modifications could be induced by altering the territory, the nature, or the mode of stimulation. Of procaine blocks the authors report that "by a judicious manipulation of the stimulus intensities used it was possible to record almost any desired order of sensory loss."

§ References 18 and 19.

‖ References 21 to 23.

In our own experience, local anesthesia with procaine makes it difficult to note any distinct successive dissociation, owing to the speed of sensory failure. Sensory loss in the fingers, induced by a sphygmomanometer cuff compressing or asphyxiating the nerves in the arm (three subjects), produces a perversion and delay in all sensations, with paradoxical tingling, stinging, and heat resulting from cold stimulation, while touch is still just perceptible. Preterminally there are hypesthesia and hyperpathia with a feeling of warmth on deep pressure. Thus, no blocking agent leaves any modality completely intact at any time while any other modality is completely abolished. There seems to be no close correlation between the differential effect on the fibers of various sizes and the effect on the traditional modalities. "Selectivity lies in the functional properties of the block rather than in the size of the fibers affected." [24]

Maruhashi and associates,[25] in recording from single afferent nerve fibers of the toad and the cat, found that certain relatively large fibers which responded to touch and pressure were insensitive to acid ("pain"), while smaller fibers were sensitive to both heat and acid, but not to touch and pressure. The small fibers had a wider receptive field in the skin, and the spots from which they could be fired were more densely distributed than was the case with the larger fibers. But the comparative fiber sizes ranged from 5μ to 11μ for "large" and from 4μ to 8μ for "small" fibers; i. e., they overlapped considerably. Nevertheless, it was found that some individual fibers were selectively responsive to some and not to all types of stimuli. Although this suggests some measure of specificity, there is no convincing relation to fiber size.

In the human tooth pulp over 50% of the nerve fibers (myelinated and unmyelinated) are smaller than 6μ. But the remaining, nearly 50%, are between 9μ and 10μ. A somewhat greater number of large myelinated fibers, including sizes over 10μ, are found in the peridental membrane.[26] The amounts of large fibers are striking in both locations, and the differences in innervation hardly sufficient for making the pulp the receptor for pain only, relegating all other sensations to the peridental membrane. This alleged division of labor has been based on the persistence of touch sensations in teeth after extirpation of the pulp (Stewart [27]; Brashear [26]; Pfaffmann [28]), a gratuitous assumption which would have to be verified by removal of the peridental membrane while leaving the pulp intact. No C-fiber activity, but only the discharge of small- and medium-sized A-fibers, has so far been recorded from the tooth pulp (Brookhart, Livingston, and Haugen [29]).

Thus, the exceptions to the rule that purports to correlate fiber size with modality are at best as numerous as those instances in which the rule seems to apply.

SPINAL CORD TRACTS

Sensory dissociation, i. e., the loss of some modalities with preservation of others, in a given area, has been correlated with injury of spinal cord structures since Fodera,¶ Schiff,[13] and Brown-Séquard.[30]. Interruption of the anterolateral spinothalamic tract reputedly abolishes three modalities—those of cold, heat, and pain—while interruption of the dorsal tracts abolishes position, vibration, and some tactile sensations.# After radical spinothalamic chordotomy for relief of pain, White and associates [31] found that various forms of deep pain were abolished in only 10% to 45% of cases, rapid pinpricks were painless in only 40%, cutaneous analgesia was

¶ Fodera, 1823, cited by Schiff.[13]

The remainder of afferent spinal tracts (anterior and spinocerebellar) are not discussed; they complicate this argument without being essential to it.

incomplete in 30%, and loss of heat sensation incomplete in 25%. On the other hand, touch was also impaired in 1 case (5%) and localization in 2 (10%); only position sense was intact in all 20 cases examined. But all 20 patients resented a painful faradic current of 40 to 140 volts. Browder and associates,[32] after dividing the dorsal spinal tracts for the relief of cramping or "postural" phantom pain, found tactile sensation unimpaired in all their six patients, a moderately impaired sense of vibration in three, and mild impairment of position sense in three, with recovery after three months. In neither study could the anatomical completeness of the interruption be verified. Schiff[13] and Foerster[33] reported pain with harmful stimulation of the dorsal tracts.

In one recent paper (Yoss[34]), the evidence favors the traditional view of specific cord tracts; another paper (Gardner and Haddad[35]) contradicts it. In the experiments of the first paper "painful" pressure applied to the exposed Achilles tendon of the monkey produced evoked potentials in the cortex despite section of the dorsal spinal tract; but, as expected, potentials were abolished after section of the anterolateral tract, with the dorsal intact. The second paper describes the unhindered, bilateral arrival of impulses in the cat's cortex upon stimulation of any kind of nerve—whether cutaneous or deep—and no matter which of the spinal tracts was divided. One could argue against the first paper that the monkey's tendons happen to have no other than spinothalamic connections, regardless of their sensory functions, and against the second, that all the nerves studied contained fibers conveying all kinds of sensation.

Division of the "pain" tract of the trigeminal nerve in the medulla oblongata produces loss of superficial pain and temperature sensation, but heavy deep pressure may be preserved, the appreciation of temperature not completely abolished, and touch mildly impaired (own observation).

From a recent report on mesencephalotomy and mesencephalothalamotomy,[36] yielding similar findings of dissociation, one suspects that the analgesia to prick, incomplete in some cases, was associated not only with hypothermesthesia but also with mild disturbances of other modalities.

Clinical experience with spinal cord disease, verified by pathological studies, shows that, despite the over-all evidence of dissociation, so useful in diagnosis, one modality or two are never either completely spared or abolished to the absolute exclusion of the others.[37] In our own experience, parts denervated by anterolateral chordotomy are reported as feeling "numb"; discrimination of two points and texture of materials is diminished, and, in addition, there are thermanesthesia and analgesia.

If large fibers were concerned only with the conduction of nonthermal and nonpainful stimuli, one should expect to find them in overwhelming numbers in the dorsal spinal tracts. Häggqvist,[38] on the contrary, found all calibers mixed, with the small fibers predominating in these, as in all other, tracts. In Goll's tract he found few fibers as large as 14μ and 15μ, the majority between 8μ and 9μ, and as many as 30% under 2μ in diameter.

The study of afferent spinal cord tracts thus does not allow an unmistakable grouping of all conducted sensations. It boils down to only two anatomical groups and fails to account for more than two types of sensory experience. These are difficult to characterize briefly. Fiber size seems altogether irrelevant.

CEREBRAL REPRESENTATION OF SENSATION

The dorsal spinal tracts enter into thalamic synapses with at least the postcentral gyrus. There is no evidence that the spinothalamic tract as a unit is to any extent relayed to the cerebral cortex. Beyond the thalamic level its continued identity has not been traced. Cortical viscerosensory representation—near or in the visceromotor area—has been shown by Amassian,* in animals. Any correspondence with any one sensory modality, especially cutaneous pain, seems remote.

Faradic stimulation of the postcentral gyrus produces tingling in the corresponding periphery,[41] but sensations of touch have never been evoked by stimulating any part of the brain, and those of hot, cold, or pain, rarely and doubtfully so. Spontaneous pain and hyperalgesia in the corresponding periphery result from strychninization and partial lesions of the thalamus, similar in character to the "burning" dysesthesia provoked by partial lesions of the posterior horns of the spinal cord or the peripheral nerves. Gross thalamic destruction leads to generalized contralateral hypesthesia. Destruction or ablation of the postcentral gyrus usually interferes only with the appreciation of postural and other spatial relationships, such as multiple simultaneous stimulations, and may lower the awareness of cutaneous stimuli in general. Ablation of the postcentral gyrus has been beneficial in the treatment of phantom limb pain.† Destruction by mesencephalotomy and mesencephalothalamotomy [36] are referred to in the previous section.

It appears, therefore, that the four modalities are not as such represented in the brain. Exclusive insensitivity to pain has been reported in rare instances. Only Schilder and Stengel [44] found this curious phenomenon in patients with parietal lobe lesions; a number of other observers ‡ reported it as a congenital anomaly of function not associated with any structural defect, or with any functional deficit in any other sphere. The condition certainly is not apt to support the specificity of peripheral pain fibers; whether it is allied to agnosia, areflexia, or hysteria and algophilia [49] remains to be seen.

GENERAL CONSIDERATIONS AND A NEW HYPOTHESIS

Classification of Function.—The conduction of a modality is a function of the nervous system. For the sake of clarification, it may be useful, if somewhat digressive, to examine some of the ways in which we define and classify functions, and some of the inherent pitfalls.

In our endeavor to correlate structure with function we are apt to forget that the two are often mutually defined. Many terms in biological nomenclature bear witness to this confusing habit. In the anatomy of muscles we speak of "flexors" and "constrictors"; among the cranial nerves we have the "olfactory," the "optic," the "acoustic." We even speak of "pain fibers," gratuitously implying that unmyelinated afferent fibers have this one function only. Although errors are thus being made, we have at least a number of accurate morphological descriptions, which allow us to classify the anatomical structures according to valid principles of shape and location.

It is far more difficult, indeed, perhaps impossible, to define and classify functions. We find that a flexor may also be a rotator, or that an unmyelinated fiber

* References 39 and 40.

† References 42 and 43.

‡ References 45 to 48.

in, say, the cornea conveys touch and its approximate local sign, as well as pain. Moreover, the definition and description of a function are usually also *ad hoc* constructions.

While structures are impervious to linguistic whims and to doubt, because they can be simply pointed to, functions are concepts of a more arbitrary and unstable kind, and surrounded by uncertainty. The main point, however, is that functions tend to become more numerous than types of structure, so that we find it necessary either to reduce the number of functions or to have different combinations of one type of structure carry out different tasks.

"Pain" and "touch" vary according to the objects producing them and to the areas stimulated; they also vary among individuals and among species.

Functions are hard to count, or set in parallel to each other, to line up and put down on a list. Moreover, the frames of reference are often on incompatible levels of abstraction. The list of four basic sensory modalities is as ill-assorted as would be a classification of paintings into, say, "landscapes," "small pictures," "large pictures," and "damaged paintings."

Classification also implies subdivision. We may, e. g., want to subdivide the sum of all instances of touch. Thus, besides size, shape, number, weight, and compressibility of the perceived object, we have to consider local sign, duration and sequence of exposure, movement, figure-background relationships, attention, "set," recognition, etc. Can each item on this ever-incomplete list of overlapping abstracts serve as an equivalent subgroup in the classification of tactile sensation? Not with any great amount of ease, especially if we consider the influence which other senses have on cutaneous perception.

Our skin sensations are never exclusively one of the four modalities but are combinations of two or three. The person subjected to the experiment has to be briefed in order to report on one modality only. The tetrad, or "straight jacket," [50] of modalities thus corresponds neither to the number of types of physical stimuli which we might single out nor to the types of sensations they purport to characterize; four are too few to correspond to an arbitrary number of types of nerve endings, and too many to fit into a dichotomy of large and small nerve fibers, or posterior and anterolateral spinal cord tracts.

Where dissociation of cutaneous sensation occurs, it is customary to compare the relative intensity of perception in one modality with that in another. While a rough method of doing this has been found useful in the clinic (e. g., in the statement, "Touch is better preserved than pain"), it is open to criticism when the criteria are made more rigorous.§ It is, naturally, impossible to find standards for comparison of such incongruous physical and perceptual parameters as those provided by kinetic and thermal energy, not to speak of an energy which we would have to call "noxious," to account for pain.

As physical objects, all parts of the body react to mechanical, thermal, and chemical "stimuli," and, being alive, they add some response of their own. Specialization of response takes place in various organs of the body and in parts thereof; e. g., a part of the hypothalamus may be more sensitive to temperature changes in the blood than other parts of the brain; through its efferent connections this part may act as a thermostat. In this sense, we can speak of "localization of function" and of "specificity." But it seems an unpromising task to look for the

§ References 15 and 51.

place in the brain that represents nothing but the sensation of, say, heat, conducted to it from any and all areas of the body.

Locoception.—While there are conceptual difficulties in assigning a place in the nervous system to any nonextended sensory quality, we have no great difficulty in having nerve structures represent physical structures—an area in the brain corresponding to one on the skin, as an object is touching it. There is, thus, one "function" that logically we might be permitted to "localize" in the nervous system. It is the function of perceiving spatial relationships in the environment, on the surface, and inside the organism. This function of apprehending extendedness, i. e., one of the classical "primary" qualities, does not explicitly figure among von Frey's four modalities, but is closely related to "touch." In its wider implications we might call it "locoception."

Probably in all organisms mechanical or any other contact with the body surface produces a reaction; the application of kinetic energy is somehow conducted and registered. Even a primitive central nervous system must, therefore, have an arrangement by which the part involved, rather than the whole organism, is made to react to the stimulus. The reaction bears the imprint of "local sign": in terms of structure, nothing more or less than a circuit in which a peripheral part is connected with a limited area in the central nervous system. In amphibians the connection is presumably made via the anterolateral tract, as they have no posterior spinal tracts to speak of, certainly no true dorsal funicular nuclei or medial lemniscus.[52] The posterior spinal tract shows a remarkable increase in size as we ascend the evolutionary scale. However, uninterrupted spinothalamic fibers are said to appear only at the evolutionary stage of the monkey; moreover, their number, segregated from spinotectal and other admixtures at the mesencephalic level, is quite small,[53] and thus apparently designed to convey spatial relationships with but little precision. Both the anterolateral and the posterior spinal tracts are thus concerned with conveying local peripheral impacts to the thalamus, but the posterior column is better equipped for the discrimination of spatial relations. These include position and change of position in any body part.

Touch is one instance of locoception. In its primary role as a local sign, it includes other sensations, such as tickle (when it is light and brief), warm, cold, wet, rough, and so forth. Heavy touch, or pressure, due to greater deformation of tissue, involves more and more deeply situated lococeptors. All instances of sensation from the skin include an element of touch, i. e., local sign.

It seems that myelinated fibers with fast conduction and low threshold, a late phylogenetic acquisition, are best, if not exclusively, equipped for the job of locoception; tissues that are poorly endowed with myelinated fibers, such as the viscera, are poor emitters of "local sign." We may take into account the numerical reduction of fibers which follows from synaptic interruptions and from the relationship of a small area of central representation with the wide distribution of peripheral endings; yet we may agree that there is a more or less detailed, "point-to-point" reception in spinal cord, thalamus, and cortex. At the top of the evolutionary scale, and for certain distal areas of the body, this representation is most detailed; in man the patterns of excitation for face, tongue, and fingers are the most subtle. Central sensory patterns are further enriched by the phylogenetic enlargement of the parietal lobe and the accessibility of impulses to other cortical association areas. Thus, all

merely spatial aspects of bodily perception are not too far beyond our understanding; i. e., they are "reducible" in terms of pathways, connections, cortical areas—structure. Discrimination in time, such as the rapid on- and off-effect in the perception of vibratory stimuli, also fits in well with the relatively fast conduction and adaptation of large fibers and with the cortical connections of the posterior spinal tracts. Impressions of time and movement are bound up with local signs evoked either repeatedly or over an extended area. We perceive and conceive time on a spatial basis, and in terms of on- and off-effects.

On physical, physiological, and anatomical grounds, therefore, it seems expedient to gather the spatial aspects of perception as they are given in touch, proprioception (including sense of balance), kinesthesia, two-point discrimination, stereognosis, and vibration into one "function": "locoception," for want of a better name. There is, however, no reason to deny to fibers of small size or to the anterolateral tract all ability of conveying information as to the where and when of stimulation, including size of area and repetition of stimulus.

Where we speak of proprioception, stereognosis, and kinesthesia, reference should be made to the important role played by the motor system in perception.[54] We think, here, of the concepts of negative feed-back,[55] of the *Gestaltkreis*,[56] and the discovery of the small motor nerve fibers which "set" muscle spindles.[57] Such reference, however, is made here only in passing, as it is not essential to our main argument.

Intensity.—Next to "local sign," and discrimination within a multiplicity of local signs, we have the function of perceiving, reacting to, and discriminating intensities. But "more" and "less" is a framework of quantity deceptive in its generality. According to physics, more energy is in the greater weight and the greater heat; here our sensations agree. But it is doubtful whether the distinction between "heavy" and "light" is quantitative or qualitative. Moreover, a "lesser" temperature feels "more" cold; eventually it produces pain, i. e., the same sensation which we get from great heat, prick, or punctiform faradic stimulation.

It has been shown that a stimulus increase in weight produces an increase in the frequency of nerve discharge.¶ But an increase in vibratory or electrical frequency does not produce a "stronger" sensation; it does not become painful. Nor are high frequencies of nerve impulses associated with sensations of pain.[60] A very low stimulus frequency is perceived not as tingling but as repeated touch; a very high one (above 450) again ceases to produce tingling unless the amplitude is raised. Only if the amplitude is raised above a certain value, regardless of the stimulus frequency, does pain result.# Consequently, with regard to the sensory effect, frequency and amplitude are not independent variables. It is the amplitude of the stimulus, however, which mainly decides the degree of unpleasantness.

Thus, with some stimuli an increase in physical energy produces a space-time increase in frequency of nerve discharge and a concomitant "more," "larger," "greater" in sensation. A greater number of fibers involved also adds to this plus on a conventional geometrical and numerical basis. At any rate, there is no specificity, in the ordinary sense of the word, of either structure or function involved here.

|| Footnote deleted on proof.

¶ References 58 and 59.

Personal observation, unpublished.

Quality.—Finally, we come to the classical "secondary," or nonextended, qualities. Even if in immediate experience these qualities are not separable from locoception, we want to account for the differential character which they acquire when they are being sufficiently obtrusive or particularly attended to. As individual nerve fibers are known to conduct only a variety of impulse frequencies, and as these account for intensities only, it has been assumed that either the size or some hitherto obscure and special (genetic?) property of nerve fibers enables them to reproduce qualitative differences. Both assumptions encounter the objections mentioned before.

Heat and Cold: Leaving aside the question of how we perceive any quality at all, we may turn to Nafe's [11] view of the mechanism by which we distinguish between hot and cold. His theory certainly deserves greater credit than it has hitherto received from physiologists. It seems to be the most advanced because it combines sensory with motor phenomena and offers some sort of conceptual unity.

Briefly, Nafe postulates that in the skin vasoconstriction, among other stimuli produced by low temperatures, influences the receptors in the capillary wall in a different way than does vasodilatation, which, among other stimuli, is produced by heat. The difference is said to be due to the degree of stretch in the nerve endings; this determines the perceived temperature.

No doubt there is close interaction between the temperature gradients in the skin when cooled or heated, and vasomotility. There is an equally close interaction between the stimulus of vasomotility and the response of vasosensibility. This closeness is reminiscent of the sensorimotor reaction to stimuli in the lowest animals and in plants, or of the axon reflex. The law of Bell and Magendie seems suspended. It so happens that only primitive, unmyelinated small fibers are present around capillary walls. What consequently decides this issue is not necessarily any intrinsic specificity of nerve elements. It is, again, a spatial anatomical relationship of axons to the contractile smooth muscle of the cutaneous blood vessel. Thanks to this relationship, which is neuromuscular and sensorimotor at the same time, we register a temperature only after the caliber of the cutaneous blood vessel has been adjusted. The nerves involved may even have both orthodromic and antidromic conduction. Thermoception is conceivable as a low form of kinesthesia—kinesthesia of an autonomic type, which we feel as, and call, warm and cold if it occurs in body surfaces. Most of the nonmyelinated, primitive fibers from blood vessels are connected with the sympathetic and anterolateral spinothalamic pathways. In order to respond, they need greater spatial and temporal summation. They carry a poor sort of discriminative locoception; they are likely to be relayed to vasomotor centers in the medulla and brain stem, and hence with arousal and stress mechanisms leading to primitive, undifferentiated skeletal defense reactions.

The work of Zotterman * and his school, however, emphasizes the specificity of cold, warm, and mechanical receptors as found in the tongue of the cat. Here, again, one is struck by the wide overlap in response. "Warm receptors" (apparently free endings) are of "somewhat" greater diameter than "cold receptors" and relatively few. They show a steady discharge with temperatures between 20 and 47 C. However, maximum frequencies are observed "usually" at 38 to 43 C in some ("warm") endings, and at 25 to 35 C in others ("cold"). Some receptors or fibers show a rapid volley of impulses when suddenly cooled; others do this when suddenly heated; they are accordingly classified as specific receptors. "Paradoxical"

* References 61 to 63.

discharge of a phasic character in response to a fall in temperature of more than 8 to 15 degrees (C) has been observed for so-called warm receptors; a paradoxical steady discharge in response to constant high temperature (45 to 50 C) was seen in so-called cold receptors. "All three types of fibers (including mechanoreceptors!) were phasically excited by local cooling of the nerve."[62] Whether the differential temperature response of single fibers, even if it were less scattered, corresponds to actual sensations is yet another matter. Zotterman does not exclude the direct action of the blood temperature on central thermosensitive structures, such as the hypothalamus.

These authors † also state that the pain produced by heat is "maintained" by the combined excitation of "cold and pain" fibers, but is "initiated" by "warm and paradoxical cold" impulses (i. e., impulses in those receptors and fibers that ordinarily respond to warm stimuli, together with receptors and fibers that ordinarily respond to cold but, paradoxically, also respond to temperatures at and above 45 C!).

Pain: The painful character of local sensations, whatever the effective stimulus, is closely related to autonomic reactions and, in experience, to sensations of "burning" heat and "aching" pressure. The anatomical conduction of pain from body surfaces has never been satisfactorily separated from that of heat, and their close association in experience also cannot be doubted. All cutaneous pain is "hot" or "burning," whatever the stimulus. ("Deep burning pain" is, in fact, throbbing, i. e., repetitive pressure.) Analgesia and thermanesthesia occur almost exclusively together when the spinothalamic pathway is interrupted. Deep aching pressure is not always relieved by anterolateral chordotomy[31]: Cramping phantom pain has been benefited by posterior chordotomy.[32] The posterior tract is painfully sensitive to mechanical stimulation.‡ Thus, not all pain is conducted by the anterolateral tract.

Pain mechanisms are also nonspecific in providing the organism with danger signals, and hence with discomfort leading to defense reactions. Not only has it often been pointed out that chronic pain is useless in this respect,§ but one should also consider that all sense organs when stimulated with sufficient intensity, or in an unaccustomed way, act as danger signals, and none better than the distance receptors.

Alarming burning and pressing sensations, i. e., those of pain, seem to originate from any of the receptors in epithelial linings and connective tissue, or in skeletal and smooth muscle, or from certain partial lesions of the conducting units in the nervous system (thalamus, lower brain stem, posterior horns, peripheral nerves[33]). The disagreeable quality is not likely to be due to any intrinsic property of any single nerve fiber, for these are probably never stimulated separately.

The discomfort is better explained by certain events that affect the normal interplay of fibers generally. Such events usually follow what might be called a "supra-adequate" stimulus. Naturally, this is a relative term, and "extra-adequate" might be preferable. In the human tooth pulp, for instance, with its mixed fibers, a loss of protective enamel turns an adequate stimulus into a supra-, or extra-adequate, i. e., painful, one. Destruction or alteration of a portion of fibers in a nerve leads to an altered pattern of synchrony in conduction, probably due to "hyper-synchronization,"[65] "simultaneous discharge of individual end organs,"[66] or "epilepsy in a peripheral nerve."[67] With the appropriate events taking place in

† References 61 and 63.

‡ References 13 and 33.

§ References 12 and 64.

connected parts of the central nervous system, pain results. Pain in any area is incompatible with "normal" functioning of that area and, consequently, of its central nervous connections. It suppresses all other sensations and produces hypesthesia and hyperalgesia.[68]

We may venture the hypothesis that the noxious stimulus inhibits parts of the orderly "out-of-phase" stream of impulses. It is, in fact, likely to impair or suppress conduction in large fibers—as it abolishes all finer discrimination in experience. The noxious stimulus, we might assume, releases, isolates, and summates the conduction mainly in small, high-threshold fibers, which have slow adaptation and a persistent after-discharge.‖ This would explain why small fibers and free endings do not always report "pain" when stimulated; they have to be isolated and thrown into hypersynchrony to do so. Pathological conditions are apt to interfere with and abolish large-fiber conduction. A high stimulus intensity rarefies and simplifies the impulse pattern. By the same token, a "mild" stimulus can produce pain in a rarefied, or injured, sensory nerve, or through rarefaction and "sensory epilepsy" in the sensory conductors of the central nervous system.

The distinction and dissociation of "pricking" and "delayed burning" pain,[71] most recently demonstrated [20] by means of experimental anoxia and procaine block, is not simply one between small myelinated delta fibers and unmyelinated C-fibers. The absence of pricking pain is, indeed, the absence of the finer lococeptive (epicritic) aspect of pain, and it is due to the inhibition of larger fibers from the skin; in the rarefied nerve the electrical current, an inflammatory lesion, or deep pressure produces pain of the delayed (protopathic) variety. But the authors themselves make the comment that in these experiments C-fibers are being *released* and *summated*. In other words, these fibers assume the function of pain conductors only when certain pathological conditions are set up in the tissue and its nerve supply. Moreover, the distinction between pricking and burning pain is dependent on the size of the area under stimulation. Lococeptive factors enter into the experience to some extent; they do so also in the perception of "deep pain."

Tickle (very light but disagreeable touch), itch (very light but disagreeable burning), and tingling (very light but disagreeable repetitive touch or pressure) are also likely to result from rarefaction, isolation, and partial inhibition of impulses in a set of nerve fibers. But in dysesthesia, due to extra-adequate stimuli, both the inhibition of large and the summation of small fibers is less marked than in pain.

Pain, although it follows nerve pathways which are present even in the invertebrates, is as "primitive" or as evolved as the organism whose cerebral cortex elaborates the afferent impulse. A human being is able to spin his fantasies around it, to experiment with its effect on himself, or to suppress the effect. Lower animals and babies display only simpler reactions to noxious stimuli, but these are also fundamentally operative in adult man. Whether or not an organism is "conscious" of a painful (or any other) stimulus depends on the general state of wakefulness, on the spread of the impulse to interpretative brain areas, and on an arbitrary terminology, which may deny consciousness and mind to lower animals.¶

Pain is an "affective quality" [74] only in the sense that it has the autonomic, hormonal, and behavioral characteristics of an emotion. It is distinguished from other emotions by having a perceived local origin in the body. But it is a physiological event for all that, and not more or less "psychological" than other nerve

‖ References 69 and 70.

¶ References 72 and 73.

processes. Pain can be classified as one of the sensations or perceptions only if we refer to experimental pain induced for the sake of introspection into feelings, or of guessing at stimulus intensities. What pain "is" depends on the aspect under which we investigate it; no results gained by one single method can exhaust its description.

The understanding of the physiology of pain is not helped by maintaining that its experience is "composed not only of pain sensation but of associated sensations and of emotional and affective states as well.[68] Such analytical features do not distinguish pain from any other sensory act, except that in most instances of noxious stimulation the subject's autonomic, hormonal, and defense reactions (as well as his "feeling states," i. e., anger, fear, pleasantness, unpleasantness) are stronger than in most instances of seeing, innocuous contact, physical exercise, etc.; the over-all disturbance of the homeostatic equilibrium is greater. Nor can "every sensation of pain (ache, prick, burn) be viewed as accompanied by a more or less predictable pattern of associated sensations (such as, heat, cold, pressure)." [68] The sufficiently short stimulation of a sufficiently small area of the skin with a heated wire, a pin, intense faradic current, or dry ice produces indistinguishable sensations of discomfort in the blindfolded subject.# The associated sensations, if present, are a result of the temporal and spatial characteristics of the stimulus-response pattern. The specificity of pain rests in the excessive, summated nature of an organism's response—and under response one has to include perception.

The difference between pain and other sensations has its parallel in the motor sphere, where we may distinguish between convulsions and orderly movements. But nobody has yet suggested the classifying of motility into a fixed number of modalities. On a phylogenetic basis, however, the distinction between protopathic and epicritic sensation [75] has some justification; i. e., it is about as valid as, and is comparable to, the distinction between extrapyramidal and pyramidal systems in the motor sphere.

The biological significance of pain is not usually exploratory, as is that of the special senses; only under very particular circumstances do organisms turn to, instead of away from, painful objects.[76]

CONCLUSION

The wealth and intricacy of those sensory experiences which are mediated by general somatic and visceral afferent systems depend on the peripheral and central location of receptors, on their connections, on the relative number of nerve units involved, on their mutual relationship in space, on the phase relationship of their impulse frequencies, on duration, intensity, and rate of increment of the stimulus, and on development or learning. Any other specificity of single, individual spots, endings, or fibers does not appear to play an essential part, or even to exist in any clearly definable sense.

If, according to present teaching, we allot pain conduction to C-fibers, possibly to visceromotor B-fibers, and to the δ group of the A-fibers, we are left with the α, β, and γ elevation of the A-group for fibers which are supposed to conduct sensations other than pain. Which are these sensations? Not thermesthesia, for this is also said to be conducted by the small fibers of the pain category. Thus, there remains only touch and proprioception, but the latter is not included in the classical tetrad of modalities. For proprioception (and motility) the α fibers of the A-group

Lewis.[64] Also, personal observation, unpublished.

have been reserved, as they are absent in cutaneous nerves. Only β- and γ-fibers, hardly distinguishable from one another, are finally left for touch. On the basis of fiber size, the only remaining "specific," identifiable modalities are, thus, touch and pain. Is it not likely, then, that the whole question of modality and fiber size boils down to intensity of stimulus, threshold, and discriminatory power in the interplay of fibers? In other words, all we can distinguish is good and poor locoception, on one hand, and asynchronous and synchronous (summated) conduction, on the other.

REFERENCES

1. Blix, M.: Experimentelle Beiträge zur Lösung der Frage über die spezifische Energie der Hautnerven, Ztschr. Biol. **20**:141, 160, 1884.

2. Goldscheider, A.: Schmerz, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Springer-Verlag, 1926, Vol. XI, p. 1.

3. Donaldson, H. H.: On the Temperature Sense, Mind **10**:339-416, 1885.

4. von Frey, M.: Beiträge zur Sinnesphysiologie der Haut: III., Ber. Verhandl. König. Sächs. Gesellsch. Wissensch., pp. 166-184, 1895.

5. Dallenbach, K. M.: The Temperature Spots and End-Organs, Am. J. Psychol. **39**:402-427, 1927.

6. Dallenbach, K. M.: Pain: History and Present Status, Am. J. Psychol. **52**:331-347, 1939.

7. Jenkins, W. L.: Studies in Thermal Sensitivity, J. Exper. Psychol. **22**:164-178, 1938.

8. Tower, S. S.: Nerve Impulses from Receptors in the Cornea, Proc. Soc. Exper. Biol. **32**:590-592, 1935.

9. Ruffini, A.: Sur les expansions nerveuses de la peau, Rev. gén. histol. **1**:421-540, 1905.

10. Goldscheider, A., and Brückner, A.: Zur Physiologie des Schmerzes: Die Sensibilität der Haut und des Auges, Berl. klin. Wchnschr. **56**:1225-1226, 1919.

11. Nafe, J. P., and Wagoner, K. S.: The Insensitivity of the Cornea to Heat and Pain Derived from High Temperatures, Am. J. Psychol. **49**:631-635, 1937.

12. Livingston, W. K.: Pain Mechanisms, New York, The Macmillan Company, 1943.

13. Schiff, J. M.: Lehrbuch der Physiologie des Menschen: I. Muskel- und Nervenphysiologie, Lahr, M. Schauenberg. u. Comp., 1858-1859, pp. 166, 206, 238.

14. Stöhr, P.: Die peripherischen Endungen der Nerven, in Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Springer-Verlag, 1928, Vol. 4, Pt. 1, pp. 217-264.

15. Sinclair, D. C.; Weddell, G., and Zander, E.: The Relationship of Cutaneous Sensibility to Neurohistology in the Human Pinna, J. Anat. **86**:402-411, 1952.

16. Hagen, E.; Knoche, H.; Sinclair, D. C., and Weddell, G.: The Role of Specialized Terminals in Cutaneous Sensibility, Proc. Roy. Soc., s. B., London **141**:279-287, 1953.

17. van der Sprenkel, H. B.: Microscopical Investigation of the Innervation of the Tooth and Its Surroundings, J. Anat. **70**:233-241, 1936.

18. Gasser, H. S.: Conduction in Nerves in Relation to Fiber Types, A. Res. Nerv. & Ment. Dis., Proc. **15**:35-59, 1935.

19. Gasser, H. S.: Pain Producing Impulses in Peripheral Nerves, A. Res. Nerv. & Ment. Dis., Proc. **23**:44-59, 1943.

20. Landau, W., and Bishop, G. H.: Pain from Dermal, Periosteal, and Fascial Endings and from Inflammation, A. M. A. Arch. Neurol. & Psychiat. **69**:490-504, 1953.

21. Sinclair, D. C., and Hinshaw, J. R.: Sensory Changes in Procaine Nerve Blocks, Brain **73**:224-243, 1950.

22. Sinclair, D. C., and Hinshaw, J. R.: A Comparison of the Sensory Dissociation Produced by Procaine and by Limb Compression, Brain **73**:480-498, 1950.

23. Sinclair, D. C., and Hinshaw, J. R.: Sensory Changes in Nerve Blocks Induced by Cooling, Brain **74**:318, 1951.

24. Denny-Brown, D., and Brenner, C.: Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch. Neurol. & Psychiat. **52**:1-19, 1944.

25. Maruhashi, J.; Mizuguchi, K., and Tasaki, I.: Action Currents in Single Afferent Nerve Fibers Elicited by Stimulation of the Skin of the Toad and the Cat, J. Physiol. **117**:129-151, 1952.

26. Brashear, A. D.: The Innervation of the Teeth, J. Comp. Neurol. **64**:169-183, 1936.

27. Stewart, D.: Some Aspects of the Innervation of the Teeth, Proc. Roy. Soc. Med. **20**:1675-1686, 1927.

28. Pfaffmann, C.: Afferent Impulses from the Teeth Due to Pressure and Noxious Stimulation, J. Physiol. **97**:207-219, 1939.

29. Brookhart, J. M.; Livingston, W. K., and Haugen, F. P.: Functional Characteristics of Afferent Fibers from Tooth Pulp, Fed. Proc. **12**:21, 1953.

30. Brown-Séquard, C. É.: De la Transmission croisée des impressions sensitives par la moëlle épinière, Compt. rend. Soc. biol. **2**:33-34, 1851.

31. White, J. C.; Sweet, W. H.; Hawkins, R., and Nilges, R. G.: Anterolateral Cordotomy: Results, Complications and Causes of Failure, Brain **73**:345-367, 1950.

32. Browder, J., and Gallagher, J. P.: Dorsal Cordotomy for Painful Phantom Limb, Ann. Surg. **128**:456-469, 1948.

33. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin and Wien, Urban & Schwarzenberg, 1927.

34. Yoss, R. E.: Studies of the Spinal Cord: 3. Pathways for Deep Pain Within the Spinal Cord and Brain, Neurology **3**:163-175, 1953.

35. Gardner, E., and Haddad, B.: Pathways to the Cerebral Cortex for Afferent Fibers from the Hind Leg of the Cat, Am. J. Physiol. **172**:475-482, 1953.

36. Spiegel, E. A., and Wycis, H. T.: Mesencephalotomy in Treatment of "Intractable" Facial Pain, A. M. A. Arch. Neurol. & Psychiat. **69**:1-13, 1953.

37. Walker, A. E.: The Spinothalamic Tract in Man, Arch. Neurol. & Psychiat. **43**:284-298, 1940.

38. Häggqvist, G.: Analyse der Faserverteilung in einem Rückenmarkquerschnitt (Th. 3), Ztschr. mikr-anat. Forsch. **39**:1-34, 1936.

39. Amassian, V. E.: Cortical Representation of Visceral Afferents, J. Neurophysiol. **14**:433-444, 1951.

40. Amassian, V. E.: Fiber Groups and Spinal Pathways of Cortically Represented Visceral Afferents, J. Neurosphysiol. **14**:445-560, 1951.

41. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**:389-443, 1937.

42. de Gutiérrez-Mahoney, C. B.: Treatment of Painful Phantom Limb by the Removal of Post-Central Cerebral Cortex, J. Nerv. & Ment. Dis. **112**:446-450, 1950.

43. Lewin, W., and Philips, C. G.: Observations on Partial Removal of the Post-Central Gyrus for Pain, J. Neurol. Neurosurg. & Psychiat. **15**:143-147, 1952.

44. Schilder, P., and Stengel, E.: Asymbolia for Pain, Arch. Neurol. & Psychiat. **25**:589-600, 1931.

45. Boyd, D. A., and Nie, L. W.: Congenital Universal Indifference to Pain, Arch. Neurol. & Psychiat. **61**:402-411, 1949.

46. Ford, F. R., and Wilkins, L.: Congenital Universal Indifference to Pain, Bull. Johns Hopkins Hosp. **62**:448-466, 1938.

47. Dearborn, G. V.: A Case of Congenital Pure Analgesia, J. Nerv. & Ment. Dis. **75**:612-615, 1932.

48. McMurray, G.: Experimental Study of a Case of Insensitivity to Pain, Arch. Neurol. & Psychiat. **64**:650-667, 1950.

49. Critchley, McD.: Some Aspects of Pain, Brit. M. J. **2**:891-896, 1934.

50. Bishop, S. H.: Neural Mechanisms of Cutaneous Sense, Physiol. Rev. **26**:77-102, 1946.

51. Cobb, S.: Cutaneous Sensibility in Cases of Peripheral Nerve Injury: Epicritic and Protopathic Hypothesis of Head Untenable, Arch. Neurol. & Psychiat. **2**:505-517, 1919.

52. Kappers, A. C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, pp. 189, 260-261.

53. Glees, P.: The Central Pain Tract, Acta neuroveg. **7**:160-174, 1953.

54. Sperry, R. W.: Neurology and the Mind Brain Problem, Am. Scientist **40**:291-312, 1952.

55. Wiener, N.: Cybernetics, or Control and Communication in the Animal and the Machine, New York, John Wiley & Sons, Inc.; Paris, Hermann & Cie, 1948.

56. von Weizsäcker, V.: Der Gestaltkreis, Stuttgart, Georg Thieme Verlag, 1947.

57. Hunt, C. C., and Kuffler, S. W.: Further Study of Efferent Small-Nerve Fibers to Mammalian Muscle Spindles: Multiple Spindle Innervation and Activity During Contraction, J. Physiol. **113**:283-297, 1951.

58. Bronk, D. W., and Stella, G.: The Response to Steady Pressures of Single End Organs in the Isolated Carotid Sinus, Am. J. Physiol. **110**:708-714, 1935.

59. Adrian, E. D.; Cattell, McK., and Hoagland, H.: Sensory Discharges in Single Cutaneous Nerve Fibers, J. Physiol. **72**:377-391, 1931.

60. Adrian, E. D.: The Physical Basis of Perception, Physiol. Rev. **10**:336-347, 1930.

61. Zotterman, Y.: Special Senses: Thermal Receptors, Ann. Rev. Physiol. **15**:357-372, 1953.

62. Dodt, E.: Differential Thermosensitivity of Mammalian A-Fibers, Acta physiol. scandinav. **29**:91-108, 1953.

63. Dodt, E.: Schmerzimpulse bei Temperaturreizen, Acta physiol. scandinav. **31**:83-96, 1954.

64. Lewis, T.: Pain, New York, The Macmillan Company, 1942.

65. Adrian, E. D.: The Effects of Injury on Mammalian Nerve Fibers, Proc. Roy. Soc., s. B., London **106**:596-618, 1930.

66. Gerard, R. W.: The Physiology of Pain: Abnormal Neuron States in Causalgia and Related Phenomena, Anesthesiology **12**:1-13, 1951.

67. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy, Arch. Neurol. & Psychiat. **39**:298-314, 1938.

68. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Pain Sensations and Reactions, Baltimore, The Williams & Wilkins Company, 1952.

69. Tower, S. S.: Unit for Sensory Reception in the Cornea, with Notes on Nerve Impulses from Sclera, Iris and Lens, J. Neurophysiol. **3**:486-500, 1940.

70. Hogg, B. M.: Slow Impulses from the Cutaneous Nerves of the Frog, J. Physiol. **84**:250-258, 1935.

71. Piéron, H.: The Sensations: Their Functions, Processes and Mechanisms, translated by M. H. Pirenne and B. C. Abbott, New Haven, Yale University Press, 1952.

72. Schiller, F.: Consciousness Reconsidered, A. M. A. Arch. Neurol. & Psychiat. **67**:199-227, 1952.

73. Abramson, H. A., Editor: Problems of Consciousness, Transactions of the Third Conference, March 10 and 11, 1952, New York, Josiah Macy, Jr. Foundation, 1952.

74. Heinbecker, P.; Bishop, G. H., and O'Leary, J.: Analysis of Sensation in Terms of the Nerve Impulse, Arch. Neurol. & Psychiat. **31**:34-53, 1934.

75. Head, H.; Rivers, W. H. R., and Sherren, J.: The Afferent Nervous System from a New Aspect (1905), Studies in Neurology, London, H. Frowde; Hodder & Stoughton, Ltd., 1920, Vol. I, pp. 55-65.

76. Pradines, M.: La Fonction du toucher, J. Psychol. norm. et path. **28**:556-639, 1931.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Meninges and Blood Vessels

HEMIPLEGIA CAUSED BY CEREBROVASCULAR THROMBOSIS: AN ARTERIOGRAPHIC STUDY. KENNETH E. LIVINGSTON, ALFONSO ESCOBAR, and GREGORY D. NICHOLS, J. Neurosurg. **12**:336 (July) 1955.

Thrombosis of an intracerebral vessel is one of the commonest causes of hemiplegia. With the advent of arteriography, internal carotid thrombosis was found to be a rather frequent cause of hemiplegia, in addition to intracerebral causes. The authors report their findings in a series of 30 patients, varying in age from 23 to 85, who were afflicted with a hemiplegic syndrome. Over one-third of the patients were over 60 years of age, and the intervals of onset of hemiplegia varied from 24 hours to 25 years. Arteriograms were done percutaneously with 35% Diodrast, and no deleterious effects were observed in any patient. The study was performed only upon those patients who had clinical evidence of progression, and it was withheld in the patients whose condition was improving.

Of the 30 patients, 18 studied showed well-defined vascular obstruction. Ten of the cases were the result of intracerebral thrombosis with arteriographic evidence of obstruction distal to the carotid siphon. Eight of the cases revealed a block of the internal carotid artery at the bifurcation of the common carotid artery in the neck or in the distal portion of the carotid siphon intracranially. The remaining 12 cases revealed no abnormalities in the arteriograms.

The authors state that their failure to demonstrate vascular occlusions in 40% of the cases may be attributable to inability to visualize the finer vascular bed. The normal arteriogram in the presence of loss of function is not inconsistent, since transient experimental occlusion of the middle cerebral artery in animals results in persisting hemiparesis, even though the blood flow subsequently appears fully reestablished.

The authors emphasize that, although a definite occlusion is demonstrable by arteriography without displacement of the vessels, there may be an infiltrating tumor of the hemisphere as a cause of the hemiplegia. Careful study of the arteriograms may reveal irregularities in the vascular pattern, in addition to the thrombosis.

MANDEL, Philadelphia.

THE COLLATERAL CIRCULATION FOLLOWING MIDDLE CEREBRAL BRANCH OCCLUSION. KEASLEY WELCH, JAMES STEPHENS, WARREN HUBER, and CHARLES INGERSOLL, J. Neurosurg. **12**:361 (July) 1955.

Occlusion of the middle cerebral artery by arteriography is characterized by failure of the vessel to fill beyond the point of obstruction and delayed retrograde filling of the cortical branches of the middle cerebral artery from branches of the anterior and posterior cerebral arteries. When the middle cerebral artery becomes occluded, the vessels distal to the occlusion fills from another major vessel rather than from the open branches of the middle cerebral artery.

The authors report two cases in which there was occlusion of the common origin of the ascending branches and the resultant collateral circulation came from the anterior cerebral branches rather than from the intact part of the middle cerebral arterial tree.

MANDEL, Philadelphia.

Diseases of the Brain

CEREBRAL COMPLICATIONS OF HYPOTENSION. JOSEPH F. FAZEKAS, JACK KLEH, and ALVIN E. PARRISH, Ann. Int. Med. **43**:165 (July) 1955.

Reversible functional disturbances, localized infarctions, and permanent loss of function of the higher centers are complications that may result from varying degrees of cerebral vascular insufficiency induced by hypotension. Cerebral arteriosclerosis may also predispose to similar disturbances. This is understandable, since in both conditions the rate of cerebral blood flow may be reduced to values below that compatible with normal cellular activity. When hypotension and cerebral vascular disease coexist, cerebral complications are more likely to occur, because their effects may be additive. Since it is practically impossible to determine the extent of cerebral

arteriosclerosis, it can be anticipated that with the use of potent hypotensive agents the incidence of cerebral complications may increase even in those subjects whose blood pressure can be maintained within normal limits.

In this report, observations of disturbances induced by varying degrees of hypotension are presented. Various cerebral disturbances, including reversible functional disturbances, cerebral infarction, shock, irreversible brain damage, and retinal damage, are discussed. Illustrative cases concerning the use of hypotensive drugs are reported.

The authors point out that the mean arterial pressure at which signs of cerebral vascular insufficiency become manifest varies considerably and is frequently highest in those subjects with cerebral vascular disease. In patients receiving hypotensive agents it may be difficult to determine whether the cerebral complication arises from a prog.ession of the vascular disease or from hypotension, since in both situations the delivery of essential substrates becomes inadequate.

ALPERS, Philadelphia.

CEREBRAL PARAGONIMIASIS. MAJOR SUN KEUN KIM, J. Neurosurg. **12**:89 (Feb.) 1955.

Paragonimiasis, or infection by the lung fluke, is endemic in Korea, Japan, and Formosa and is acquired by man through the ingestion of raw fresh-water fish. The disease may involve the lungs, pleura, liver, intestinal wall muscles, testes, and, rarely, the brain. Kim reports four cases in Koreans, ranging in age from 8 to 32 years. Three of the four patients were infected before 12 years of age. These cases were characterized by focal Jacksonian seizures, expressive aphasia, lowered intellectual ability, and double vision. Roentgenograms of the skull revealed multiple calcified nodules, and a pneumoencephalogram in one case demonstrated a space-occupying lesion. Operation in all cases revealed multiple cysts involving the frontal, temporal, and parietal lobes in one hemisphere only. No cerebellar lesions were found in any cases. All the cysts were thick-walled and contained the ova of Paragonimus westermani. Three of the patients improved after surgery.

MANDEL, Philadelphia.

HYDATID CYSTS OF THE BRAIN. ROMÁN ARANA-IÑIGUEZ and JORGE SAN JULIÁN, J. Neurosurg. **12**:323 (July) 1955.

Hydatid disease caused by the Taenia echinococcus occurs in Australia, Africa, and portions of South America. It is usually associated with the raising of sheep and cattle, and infection with the disease occurs through the ingestion of dog feces containing echinococcus rings. The ring then delivers eggs upon reaching the intestinal tract, freeing a hexacanth embryo, which passes through the intestinal wall into the liver and lung. Only 2% of hydatid cysts are found in the brain, and they are nearly always solitary. The cerebral cysts occur most commonly in the parietotemporo-occipital region, and rarely in the frontal lobes. Microscopically the hydatid cyst consists of the parasite, a hyaline membrane limited by an adventitia, and the germinative membrane. The vessels assume an arrangement parallel to the cyst. Gliosis and fibrosis occur about the cyst wall.

In the series of 13 cases reported by the authors, 10 were children 15 years or younger, and the remaining 3 were adults. The symptoms include headache, vomiting, diminished visual acuity, hemiparesis, somnolence, and convulsive seizures, headache being the earliest presenting symptom. Neurologic examination may reveal papilledema, optic atrophy, hemiparesis, signs of cerebellar dysfunction, and homonymous hemianopsia. Hydatid cysts must be differentiated from tumors of the hemisphere, and one of the most helpful diagnostic tests is arteriography. This method not only presents a characteristic radiographic picture of the blood vessels along the upper surface of the cyst, with displacement of the vessels and absence of vessels within the lesion, but offers the great advantage of preventing rupture of the cysts, which may occur when ventriculography is attempted. The surgical techniques are based upon the principle of removal of the cyst without rupture in order to prevent the formation of daughter cysts. All 13 patients underwent surgery and are alive at present.

MANDEL, Philadelphia.

CRANIOPHARYNGIOMA (PITUITARY ADAMANTINOMA) IN PATIENTS MORE THAN 60 YEARS OF AGE. JOSEPH WITT, COLIN S. MACCARTY, and F. RAYMOND KEATING JR., J. Neurosurg. **12**:354 (July) 1955.

Craniopharyngiomas are thought to arise from epithelial rests which persist from the stalk of Rathke's pouch during embryonic development, and hence the majority of tumors occur in

childhood or early adult life. The occurrence of this type of tumor beyond the age of 60 is rare. The authors report cases of craniopharyngioma in a patient aged 70 and a woman aged 63. The presenting symptoms in each case were visual in nature and consisted of loss of visual acuity, with bitemporal hemianopsia in one case. Neither case had evidence of pituitary or adrenal insufficiency prior to operation. Both patients have had striking recovery of vision following surgery and are being maintained on small doses of adrenal substitution therapy.

MANDEL, Philadelphia.

HEREDITARY COMBINED NEURINOMAS AND MENINGIOMAS. LEO M. DAVIDOFF and JOHN MARTIN, J. Neurosurg. **12**:375 (July) 1955.

Von Recklinghausen's disease in the form of multiple neurofibromatosis affecting cranial and spinal nerve roots has been shown to have hereditary tendencies. Davidoff and Martin report two such cases, the first of which occurred in a physician who was first seen by Cushing and described in his monograph on meningiomas. In both patients bilateral deafness was present, and in each a neurinoma was suspected. A tumor removed from the cerebellopontine angle in the father had the microscopic appearance of whorl formations with palisading, suggesting a mixed type of tumor. In addition, he had a large intracranial meningioma and several smaller meningiomas.

The daughter of the first patient had a history of progressive weakness of the legs with a sensory level at T 10 at the age of 15. At operation, a tumor having the microscopic appearance of a meningioma was removed from the thoracic canal. At 20 years of age she had symptoms of bilateral deafness and signs of a posterior fossa tumor. A neurinoma was removed, and the patient died one month after her discharge from the hospital. Autopsy revealed countless small meningiomas beneath the dura, as well as a tumor in the cerebellopontine angle, which had the same microscopic appearance of the mixed tumor removed from her father.

MANDEL, Philadelphia.

INTRACRANIAL BOECK'S SARCOID TUMOR RESEMBLING MENINGIOMA. S. A. SKILLICORN and RICHARD W. GARRITY, J. Neurosurg. **12**:407 (July) 1955.

Involvement of the central nervous system by sarcoidosis is uncommon, and intracranial sarcoidosis simulating a brain tumor is rare. Skillicorn and Garrity report the occurrence of intracranial Boeck's sarcoid in a 19-year-old Negro youth who had papilledema, olfactory hallucinations, psychomotor seizures, déjà vu phenomena, and slight left-sided pyramidal tract signs. Roentgenogram of the skull revealed an enlarged sella turcica with demineralization of the clinoid processes. An electroencephalogram revealed a right temporal lobe focus. Arteriography revealed elevation of the right middle cerebral artery. At operation, a large tumor with the gross appearance of a meningioma was found projecting from the floor of the middle cranial fossa, compressing the right temporal lobe but not invading it. Histologic examination proved it to be Boeck's sarcoid, with granulomatous tissue composed of numerous small nodular masses of epithelioid cells separated by lymphoid tissue. Subsequent studies to determine evidence of systemic sarcoidosis was negative except for increased serum globulin.

MANDEL, Philadelphia.

SIGNS OF OBSTRUCTION OF THE SUPERIOR LONGITUDINAL SINUS FOLLOWING CLOSED HEAD INJURIES (TRAUMATIC HYDROCEPHALUS). J. PURDON MARTIN, Brit. M. J. **2**:467 (Aug. 20) 1955.

Martin calls attention to a small group of cases of closed head injury which he thinks have been slow to receive general recognition. In these patients signs of intracranial pressure develop usually at an interval following the head injury without signs of severe intracranial bleeding, and the patient ultimately recovers without operation. The condition is similar to otitic hydrocephalus, and Martin believes that it is due to the same disturbance, that is, complete or partial obstruction of the superior longitudinal sinus. This gives rise to two syndromes, one similar to that of otitic hydrocephalus and the other a paralytic syndrome. He reports four cases of the former type and one of the latter. He considers the most important factors responsible for the sinus thrombosis to be damage to the dura in the wall of a sinus and extension of thrombosis inward from abrasions of the scalp or damaged emissary veins.

ECHOLS, New Orleans.

Diseases of the Spinal Cord

THE SYNDROME OF ACUTE ANTERIOR SPINAL CORD INJURY. RICHARD C. SCHNEIDER, J. Neurosurg. **12**:95 (March) 1955.

The syndrome of anterior cervical cord injury which follows acute trauma to the cord is characterized by an immediate complete paralysis below the site of the lesion, associated with a level of hypalgesia and hypesthesia at the level of the lesion with preservation of motion, position, touch, and, occasionally, vibration sense. In the cases reported by Schneider, the syndrome was associated with an isolated herniated cervical disc in one case, with herniated cervical disc and fracture-dislocation of the cervical spine in two cases, with fracture-dislocation alone in six cases, and with compression fracture of the cervical vertebra in one case. In two cases anterior spinal cord destruction was seen at necropsy. In one instance there was a thoracic cord injury, which was associated with double fracture-dislocation.

The author reports 13 cases of the syndrome of acute anterior spinal cord injury and stresses that it is impossible to differentiate those patients who have anterior cord compression with restriction of posterior cord displacement by the dentate ligaments from those who have anterior cord destruction. Early operation is therefore advised, with section of the dentate ligaments and inspection of the interspaces for a surgical lesion. In this series, the patients underwent surgery from 18 hours to 4 years after injury, and a most striking result was obtained in one case, in which cervical laminectomy with section of the dentate ligaments resulted in movements of the extremities when the patient had been paralyzed for a period of five and one-half weeks. Myelography was contraindicated in this group of patients for fear of causing further damage to an already injured cord.

When the patients had an acute cervical flexion fracture ("tear-drop fracture," or "diver fracture"), they were placed immediately in skeletal tong traction upon an anterior Stryker frame. Surgery was deferred in lesions at the level of the phrenic segments, C 3 and C 4, until respiratory difficulties were stabilized. Laminectomy was then performed, followed by spinal fusion in three weeks, in order to prevent movement and continued irritation to the cord.

The author states that early surgical intervention will prevent prolonged anoxia by direct cord compression and facilitate recovery, since these patients have attained their maximum neurological deficit and they do not present the usual criteria for surgery, namely, progression of neurological signs with evidence of subarachnoid block.

MANDEL, Philadelphia.

OCHRONOSIS ASSOCIATED WITH DEGENERATION OF AN INTERVERTEBRAL DISC. ROBERT S. FISHER and JOHN WILLIAMS, J. Neurosurg. **12**:403, (July) 1955.

Ochronosis is a condition in which the cartilages of the body appear black rather than white. Ocher pigment may be deposited in the hands, ribs, and large joints and is found in many tissues, such as the heart, kidneys, and sweat glands. This disease is associated with the presence of homogentisic acid in the urine, as a result of incomplete metabolism of the amino acids phenylalanine and tyrosine. Upon exposure to air or alkalization, the urine turns black, and this has been called alcaptonuria.

The authors report the case of a 32-year-old white man who had signs and symptoms indicative of a disc lesion at the right lumbosacral joint. At operation, a black cartilaginous material was removed from the disc space, and his postoperative course was uneventful.

The authors conclude that ochronosis may be responsible for destruction and pigmentation of the intervertebral cartilage, which may lead to rupture of an intervertebral disc. A preoperative laboratory diagnosis can usually be made by urinalysis.

MANDEL, Philadelphia.

CONGENITAL SPINAL EXTRADURAL CYST. BURTON L. WISE and JACOB J. FOSTER, J. Neurosurg. **12**:421 (July) 1955.

Congenital spinal extradural cysts are of congenital origin and frequently simulate tuberculosis of the spine when they occur in the thoracic region, or a herniated disc in the lumbosacral area. These cysts arise either as a congenital diverticulum of the dura mater or by a herniation of the arachnoid through a congenital defect in the dura mater. The average age group in a review of 33 reported cases was 22.6 years, males being affected more than females. Slight to marked evidence of kyphosis dorsalis juvenilis was present in 19 cases, and in each of the cases the extradural cyst was present in the thoracic region.

The authors report a case of a 29-year-old Chinese man who had symptoms and signs of a lumbar disc syndrome. Roentgenograms revealed widening of the interpedicular space of T 12 and erosion of both T 12 pedicles and left L 1 and L 2 pedicles. At operation an extradural cyst was removed, which had caused the erosion of the pedicles and the widening of the interpedicular spaces. The authors emphasize the importance of careful myelography in lumbar disc syndromes in order to exclude this lesion.

MANDEL, Philadelphia.

LYMPHOSARCOMA OF THE SPINAL EPIDURAL SPACE IN A SEVEN-YEAR-OLD CHILD. ERNST A. RODIN, HENRY W. DODGE, and ALVIN B. HAYLES, Proc. Staff Meet. Mayo Clin. **29**:571 (Oct. 27) 1954.

This case is reported because of the youth of the patient, the rapid progression of the illness, the interesting problem in differential diagnosis, the aggravation of symptoms after spinal puncture, and the satisfactory result obtained after prompt institution of appropriate treatment.

A 7-year-old girl first complained of pain in the midportion of her back, radiating around the waist. One week later weakness of the legs developed, so that by the end of the second week she was unable to walk alone. Because of the youth of the patient and the rapid progression of symptoms, and also because of the history of an acute tonsillar infection at the onset of the disease, a neuronitic process of the Guillain-Barré type was considered in the differential diagnostic survey. A diagnostic lumbar puncture was done the morning after the patient's admission. It became evident in the course of the day that a definite rapid increase in the objective neurologic signs had taken place, apparently attributable to the removal of spinal fluid and the changes in pressure relationships within the spinal cord. A iophendylate (Pantopaque) myelogram revealed complete obstruction to the cephalad flow of oil at the 10th thoracic vertebra. Laminectomy was carried out immediately, and an extradural tumor, which proved to be a lymphosarcoma, was found. Extensive subtotal resection of the tumor and wide bony decompression were carried out. The postoperative course was uneventful, and intensive deep roentgen therapy was started 10 days after operation. The child was dismissed one month after admission, showing striking improvement.

At no time during her stay in the hospital was evidence found to suggest the presence of neoplastic tissue in other parts of the body. However, a recent reexamination disclosed that the patient now has clinical and laboratory findings of generalized lymphosarcomatosis.

ALPERS, Philadelphia.

AN INTRASPINAL DERMOID CYST ASSOCIATED WITH ANOTHER IN THE OVARY. B. RAMAMURTHI and V. C. ANGULI, J. Neurol. Neurosurg. & Psychiat. **17**:225 (Aug.) 1954.

The authors describe the case of a girl aged 19 who was admitted because of inability to walk properly, dribbling of urine, and an ulcer in the sole of the left foot. The history of symptoms extended over a period of 10 years. After study a clinical diagnosis of a tumor of the cauda equina was made. On examination of the abdomen, a rounded, firm mass was felt in the hypogastrium. The mass was mobile and felt to arise out of the pelvis.

Two operations were performed. At the first procedure a lumbar intraspinal dermoid cyst arising from the filum terminale was removed. The patient had an uneventful postoperative recovery and began to show signs of gradual improvement in power and control of micturition. The ulcer in the left heel healed after a month. At this time a laparotomy was performed and a benign cystic dermoid arising from the right ovary was removed.

ALPERS, Philadelphia.

Treatment, Neurosurgery

CEREBRAL VASCULAR DISEASES. I. S. WRIGHT and E. MCDEVITT, Ann. Int. Med. **41**:682 (Oct.) 1954.

Experience with the use of anticoagulants in the reduction of thromboembolic episodes in 57 patients treated for a total period of 1.162 months is summarized by Wright and McDevitt. During a period of 795 patient-months before beginning anticoagulant therapy 57 patients experienced 205 thromboembolic episodes, 81 of which were cerebral in location. Following institution of anticoagulant therapy, during a period of 1.162 patient-months, these patients experienced 23 thromboembolic episodes, 6 of which were cerebral in location. The reduction

appears to occur in emboli arising from thrombi in the hearts of patients with rheumatic heart disease or from acute myocardial infarction. A reduction in the incidence of thromboses in the arteries of the brain was also noted.

The authors note that the risk from hemorrhage in the treatment of these diseases with anticoagulants is present, but is not excessive.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

RADIOLOGICAL CRITERIA AND FAMILIAL OCCURRENCE OF PRIMARY BASILAR IMPRESSION. J. W. D. BULL, W. L. B. NIXON, and R. T. C. PRATT, Brain **78**:229, 1955.

Primary basilar impression is a skeletal malformation involving the relationship between the cervical spine and the base of the skull. It varies in degree in different patients and occurs both with and without neurological symptoms. Chamberlain's line, drawn from the dorsal lip of the foramen magnum, has previously served as a method of determining the existence of platybasia, the odontoid process being above this line. McGregor modified this standard by introducing a measurement from the upper surface of the posterior edge of the hard palate to the most caudal point of the occipital curve in the true lateral roentgenogram.

The authors report another method of determining platybasia which they consider to be more reliable than either of the previously described methods. They measured the angle (B) between the plane of the hard palate and the plane of the atlas to determine the degree of basilar impression. The mean values and standard deviations of these three measures for the general population were estimated from 120 normal persons, and an arbitrary and provisional criterion was set up on statistical grounds. With this method, 20 patients had radiological evidence of platybasia, although 10 had no symptoms clinically, 7 had syringomyelia, and 3 had signs and symptoms which could be explained by a lesion at the level of the foramen magnum. Examination of 39 relatives of these 20 patients was made by roentgenograms, and the methods of determining platybasia were used. By means of the authors' method, 28 were found to be normal, and 11 abnormal, but the discrimination between the normal condition and platybasia was not as clear with the other methods.

The findings are compatible with the tentative hypothesis that primary basilar impression is a genetically determined skeletal abnormality which is best determined by means of the angle between the plane of the hard palate and the plane of the atlas.

MANDEL, Philadelphia.

ANGIOGRAPHY IN THE MANAGEMENT OF INTRA- AND SUPRA-SELLAR TUMORS. R. A. MONEY and G. K. VANDERFIELD, J. Neurosurg. **12**:203 (May) 1955.

Arteriography is a helpful diagnostic aid in differentiating tumors in the supra- or intrasellar area from aneurysms of the internal carotid artery. Tumors in this area result in displacement of the anterior or middle cerebral vessels. In cases of intrasellar tumors, the intracranial portions of the internal carotid artery is elongated and the "siphon" is opened out, while the terminal portions are displaced laterally and forward. The anterior cerebral arteries are displaced upward and form an obtuse angle with the internal carotid artery. In suprasellar tumors and tumors of the olfactory groove, the anterior cerebral arteries are displaced upward and backward to form a large curve with concavity forward instead of convex. In third ventricle tumors, in which the sella is enlarged, the angiogram shows the elongated anterior cerebral arteries curving around the dilated anterior horns of the ventricles. However, if the sella is not enlarged in third ventricle tumors, the "siphon" portions of the internal carotid artery are normal, but the normal curve of the anterior cerebral arteries is opened out, indicative of hydrocephalus. Frequently, aneurysms of the internal carotid artery become large enough to erode the sella turcica and produce headaches, visual impairment, and bitemporal hemianopsia, thereby simulating a pituitary adenoma. Arteriography is of greatest value in differentiating these lesions and for preparing the best surgical approach for the lesion.

MANDEL, Philadelphia.

USE OF 25 PER CENT IODOPYRACET (DIODRAST) IN CEREBRAL ANGIOGRAPHY. D. L. SUTHERLAND, WILLIAM C. KITE JR., J. F. ROACH, and ELDRIDGE CAMPBELL, J. Neurosurg. **12**:223 (May) 1955.

In an effort to find a safer contrast medium for carotid angiography, 25% iodopyracet (Diodrast) was used instead of the usual 35% solution, in 108 angiograms in 87 patients, ranging in age from 18 to 56 years. This contrast medium was found to be adequate in all but a few

instances, and it proved to be a far safer medium, as fewer complications were encountered. There was no instance in which death was hastened by angiography, although 12 patients died of progression of their disease. In one case marked spasm of the right internal carotid artery was noted at operation a few hours after angiography, and in a second case right hemiplegia with aphasia occurred 24 hours after injection.

The authors state that in a previous series, of 234 angiograms, in which 35% iodopyracet (Diodrast) was used there were approximately 167 major and minor neurological complications, in contrast to less than 2% complications with 25% iodopyracet (Diodrast).

MANDEL, Philadelphia.

IMPORTANCE OF THE DEEP CEREBRAL VEINS IN CEREBRAL ANGIOGRAPHY. PAUL M. LIN, JOHN F. MOKRIHISKY, HERBERT STAUFFER, and MICHAEL SCOTT, J. Neurosurg. **12**:256 (May) 1955.

Cerebral angiography has compared favorably with pneumoencephalography in the diagnosis of most space-occupying lesions, except in cases of deep-seated supratentorial and infratentorial lesions, where air studies may be superior. The reason for this deficiency is the fact that the larger branches of the arterial system do not penetrate to the deeper structures. However, the deep cerebral veins are often visualized in routine cerebral angiography, especially the internal cerebral vein and its branches which drain the deeper cerebral area. These veins are constant in their appearance and anatomical location, and hence are of important value in the diagnosis of deep-seated cerebral lesions.

The great cerebral vein (of Galen), the inferior sagittal sinus, and the straight sinus (sinus rectus) are attached to the falx and tentorium, so that they do not change their position in space-occupying lesions. The internal cerebral vein and its branches, however, are more vulnerable in changing their configuration with any sizable space-occupying lesion. The internal cerebral vein is readily compressed or stretched away from its fixed dorsal attachments, and the change of the angle formed by the striothalamic vein and the internal cerebral vein is known as the "venous angle" of the brain. Large space-occupying lesions of the periphery of the cerebral hemisphere can also displace the internal cerebral vein and the foramen of Monro, as visualized by the "venous angle." A tumor of the frontal lobe displaces the internal cerebral vein and venous angle posteriorly, while a neoplasm of the convexity would depress the internal cerebral vein. Occipital tumors displace the "venous angle" anteriorly.

Since visualization of the cerebral veins can be obtained in 75% of cerebral arteriograms, the authors believe that special attempts should be made to obtain a satisfactory phlebogram when a deep-seated cerebral lesion is suspected.

MANDEL, Philadelphia.

THE MYELOGRAM IN AVULSION OF THE BRACHIAL PLEXUS. A. A. RAYLE, B. B. GAY, and J. L. MEADORS, Radiology **65**:65 (July) 1955.

Rayle, Gay, and Meadors report the case histories of nine patients who were injured and who had clinical symptoms of damage to the brachial plexus. All nine patients had cervical myelograms performed, and in all nine there was an appearance in the myelograms which the authors consider pathognomonic of avulsion of the nerve roots of the brachial plexus.

In the cervical region the nerve roots are enclosed in an extension of dura mater, called the root pouch. The subarachnoid space does not extend distal to this pouch. Consequently, in the normal subject only the pouch, and never the root sleeve, is visualized in the cervical myelogram. When a injury occurs so that the shoulder is pushed down and the head pushed away from the shoulder, avulsion of the roots of the brachial plexus can occur. It is possible to have avulsion of a nerve root without any tear in the subarachnoid or dural membrane. Jaeger and Whitely have reported two such cases in which the cervical myelogram was normal. Intradural surgical exploration of the brachial plexus is necessary in these cases to evaluate the extent of damage. In the usual case, however, avulsion of the nerve roots is accompanied by tearing of the dura and arachnoid membranes at the root pouch. The opaque medium then is able to flow from the normal subarachnoid space into a small pocket in the neural foramen between the vertebrae. The appearance of the opaque medium in such a pocket is considered characteristic of avulsion of the brachial plexus.

Rayle, Gay, and Meadors believe that surgical correction of such a deformity is not possible when avulsion can be demonstrated in the myelogram.

WEILAND, Grove City, Pa.

News and Comment

GENERAL NEWS

V. A. Residencies in Psychiatry.—The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers, as well as an Annual Institute at this hospital. Training may commence at any time.

Correspondence may be addressed to M. P. Rosenblum, M.D., Director, Professional Education.

ANNOUNCEMENTS

Workshop Seminars in Rorschach Test.—The Department of Psychology of the University of Chicago announces two workshop seminars in the Rorschach Test.

I. Basic Processes. Obtaining and scoring the test record. How to translate the raw free associations into the response categories, and how these interact to form the personality structure. Full case interpretation will be demonstrated. July 9-13, 1956.

II. Advanced Clinical Interpretation. The very disturbed younger child; the test's prediction and the child's course. Stress, defense, and ego in adolescents and in adults (nonpsychotic). Treatment assets and implications. July 16-20, 1956.

Dr. S. J. Beck will conduct both seminars. For full information, write to the Department of Psychology, The University of Chicago, Chicago 37.

Books

On Aphasia, a Critical Study. By Sigmund Freud; authorized translation by E. Stengel. Price, $3.00. Pp. XV-105. International Universities Press, Inc., 227 W. 13th St., New York, 1953.

There has been a tendency, especially in the American literature, to an exaggerated adulation of Freud. That "Freud discovered the mind and divested it of its mysteries" (Brill, A. A.: Professor Freud and Psychiatry, *Psychoanalyt. Rev.* **18**:246 [July] 1931) or that Freud's character did not contain "even some pardonable human weaknesses" (Simmel, E.: Sigmund Freud, the Man and His Work, *Psychoanalyt. Rev.* **9**:174 [April] 1940) is such a manifest overstatement that the reader pauses with some wonderment. For it does not take much psychological astuteness to suspect some unconscious factors underlying exaltations of this kind, especially when they are about a man whose genius and whose contributions to the psychological welfare of mankind are undisputed.

A similar mechanism must be at work with writers who insist on claiming that everything that Freud wrote was "original" and try to portray him as prophet in possession of some mysterious revelation. That this is not so should be obvious. Freud was a scientist. All of his theories rest to some extent on work done by other scientists with whose work he was familiar. To his credit is the fact that he was able to discard the useless theories and to put to new uses some of the old ones. It would not occur to anyone to credit Einstein with the invention of mathematics in order to insure that the theory of relativity is properly attributed to him.

A good example of the latter tendency is Stengel's authorized translation of Freud's study on aphasia (Freud, S.: Zur Auffassung der Aphasien: Eine kritische Studie, Leipzig & Wien, F. Deuticke, 1891).

As a translation this is creditable. Any attempt to translate Freud's use of philosophical concepts is, to say the least, difficult, especially in this paper, where he does not seem to

differentiate between perception, image, concept, or idea and uses the word *Vorstellung* in so many different contexts that even a Lockean would be confused.

It is not the translation, however, but Stengel's introduction, that stimulated the present review. It is so full of errors and contradictions that its call for comment is irresistible.

Dr. Stengel claims that Freud was stimulated to the study of the subject by a paper by Exner and Paneth (page x). In a footnote, he obligingly gives the date of the paper as 1887. But, on page 66, Freud states that he had reported the main contents of this study at the *Wiener physiologischer Club* (sic) as early as 1886.

That Freud in his book uses the words *Besetzung* and *besetzen* is not sufficient justification to demand consideration for it "as the most significant forerunner of the author's later work" (page x). These expressions were used by Herbart, Meynert, Brücke, and practically every physiological psychologist in those days. As a matter of fact, Dorer (Dorer, M.: Die Geschichtliche Grundlagen der Psychoanalyse, Leipzig, Meiner, 1932) based her whole thesis on the similarity of vocabulary between Freud and Meynert.

Dr. Stengel also states: "Freud was the first in the German speaking world to subject the current theory of localization to a systematic critical analysis. In challenging both a powerful scientific trend and its most influential representatives he showed himself an independent thinker of considerable courage" (page x).

This statement is worth some consideration. Freud had the potentiality of genius. But, for this potentiality to become realized, he needed a stimulus. This was provided by his urge to correct some respected father figure—and so his earlier neurological papers were thus "corrections" of Paneth and Fleischl; the "Aphasia," of Meynert; his "Project," of Exner, and, finally, his "Studien," of Breuer (Jones, E.: The Life and Work of Sigmund Freud: The Formative Years and the Great Discoveries, 1856-1900, New York, Basic Books, Inc., 1953).

Nor did Freud pick the topic of aphasia out of the clear sky. Just as hysteria was of interest to medical practitioners in those days, aphasia was subject to much investigation by neurologists. Charcot was especially interested in aphasia.

There is something about this study, though, that is prescient of Freud's later psychoanalytical writings—not in his stressing psychology for the first time; that, as will be seen in a moment, had been done before him. Freud's study on aphasia shows a departure from his previous method of presentation in that he gives unusually few references to precursors. This is a characteristic that has been evident and commented upon in his later psychoanalytical writings.

On page 83 of his aphasia study, Freud makes a very fleeting reference to Ballet (Ballet, G.: Le langage intérieur et les diverses formes de l'aphasie, Paris, no publisher, 1886; translated into German by P. Bongers: Die innerliche Sprache und die verschiedenen Formen der Aphasie, Wien, F. Deuticke, 1890). Since Ballet's book represented the official Charcot view in those days, a short review of it may be of interest.

The first part of the book undertakes to present some psychological aspects of speech disturbances. Ballet stresses the need to connect psychological analysis with clinical observation, that is, the use of both psychological and biological methods. Psychologically, Ballet states, the "word" is a "collective concept," consisting of a "sound image," a "visual-letter image," and the "glosso-kinaesthetic," and the "cheiro-kinaesthetic" images or impressions.

The predominant use of any one of these images will determine the kind of aphasia to which they may succumb. Thus, people who think predominantly by the "sound image" will experience word deafness; the loss of the "visual-letter image" will result in word blindness, and so on.

In contrast to the then prevailing German localization theories, Ballet stresses the differentiation of these four basic types (*Idealtypen*), which, according to him, makes for easy comprehension of aphasia.

Ballet flatly refuses to recognize the existence of anatomical centers in the cerebral cortex that would account for the different forms of aphasia. He feels that the predominance of a specific image in the collective concept of words and thinking is due to psychological reasons: predisposition (*Anlage*) and training (*Ausbildung*).

Though he generally feels that the main forms of aphasia are psychologically determined, Ballet, like Freud, ends by assigning a center in the cortex for each of the four main aphasias, providing both psychological and physiological signs for differential diagnoses.

This short review will be sufficient to point out that Freud was, indeed, not the first one who attacked the localization theory, a concept which was advocated in those days mainly by Wernicke and Meynert, nor was he the first one who recommended the investigation of the psychological aspects of aphasia.

How much the German physiological psychologists were preoccupied with the problem of aphasia can be seen from a perusal of the titles in the *Zeitschrift für Physiologie* and the *Zeitschrift für Psychologie und Physiologie der Sinnesorgane*. The last-mentioned periodical was published by Ebbinghaus in 1890. In his own words, the journal was dedicated exclusively to psychology, and only to the aspects of neurology which are related to psychology, i. e., the physiology of the sense organs. "This limitation," continued Ebbinghaus, "will be better understood if the names of the people who so willingly accepted the editorship and gave their cooperation are considered." The editors referred to were Aubert, Exner, Helmholtz, Hering, Kries, Lipps, G. E. Müller, Preyer, Stumpf, and Pelman. Besides the editors, the following were some of the contributors: Jelgersma, Bechterew, Maudsley, Jerusalem, Munsterberg, Dubois, Eichhorn, Paneth, Meynert, Moebius, Fleischl, and Brentano.

Knowing of Freud's predilection to "study from monographs and journals," and of his relationship to some of the people connected with this publication, it is hardly conceivable that Freud did not read the *Zeitschrift*. As a matter of fact, if one is willing to relinquish the need to consider Freud as the originator of everything related to psychology, one will find that his interests were for a long time parallel to the contents of this journal.

In pointing out the similarity between Ballet and Freud on the question of aphasia, one does not detract in any way from Freud's scientific accomplishments. Freud moved with his times, and his scientific thinking was characteristic of the *Zeitgeist*. The development of psychoanalysis will make him immortal without the necessity of attributing omniscience to him.

RUDOLPH J. BRANDT
School of Psychology
University of Ottawa

Interpretation of Schizophrenia. By Silvano Arieti. Price, $6.75. Pp. 552, with illustrations. Robert Brunner, 1212 Avenue of the Americas (near 48th St.), New York 19, 1955.

In this work, Dr. Arieti writes with skill and lucidity about the schizophrenic syndromes. He brings to it a great deal of experience, extensive knowledge of the literature, and an earnest attempt to provide a simple, logical, multifocal overview. In this he succeeds admirably.

The first section deals with a critical evaluation of historical concepts in the field. The psychodynamics of schizophrenia are then discussed, with emphasis on errors in child development, particularly in the areas of self-esteem and self-identity. He then goes on to the formal mechanisms in the psychological structure of schizophrenia, discussing the patients' retreat from reason, from society, and from emotions, as they regress to avoid intolerable anxiety in intrapersonal relations.

He clarifies the schizophrenic thinking processes, taking away, happily, much of the awe and strangeness from schizophrenic productions. We use Aristotelian logic in our thinking. The schizophrenic uses what Arieti calls paleologic, in which identity based on identical subjects is replaced by identity based on identical predicates. Perceptualizations replace conceptualizations; associations by similarity are replaced by associations by contiguity, and these, in turn, are replaced by paleological identifications and thus may appear unintelligible to us. As the schizophrenic uses paleologic, so, too, he uses paleosymbols. As he gives up the ability to abstract, he loses use of current social symbols, adopting archaic paleosymbols, thus becoming desymbolized and desocialized, and hence unable to experience emotion, which has to be in terms of symbols. He can experience it via paleosymbols, but as he progressively regresses, he loses that ability, too. Many clinical examples of these processes are given.

Arieti describes this illness longitudinally as well, pointing out the various stages of the regression. He evaluates the findings of physiological investigations, seeing the abnormalities as results rather than as causes of the basic disorder.

This book is not only an interpretation, but an evaluation and a synthesis, of current thinking in the field. With the background described above, he then defines schizophrenia as "a specific reaction to an extreme state of anxiety, originating in childhood, and reactivated later in life by psychological factors. The specific reaction consists of the adoption of archaic mental mechanisms, which belong to lower levels of integration. Inasmuch as the result is a regression to, but not an integration at lower levels, a disequilibrium is engendered which causes further regression, at times to levels even lower than the one in which certain perceptions are possible."

He concludes with a section devoted to therapy. He basically favors psychotherapy, but is well aware of the value of shock therapies in specific instances. He discusses principles and

pitfalls of psychotherapy. Psychosurgery is dismissed as unacceptable: "We cannot feel authorized, therefore, to barter a permanent damage for one which is not."

This is a scholarly and comprehensive study. It is well published and has an excellent bibliography. It will be of great value to all who deal with schizophrenics, but particularly to the younger, more inexperienced, workers in the field, who often feel overwhelmed by the seeming bizarreness of their patients, and thus easily become discouraged. This volume should go a long way toward promoting understanding, sympathy, and skill.

The Cerebrospinal Fluid. By S. Lups and A. M. F. H. Haan, M.D.; translated by Mrs. Hulbert and R. S. Hulbert, with introduction by Pearce Bailey, M.D. Price, $9.50. Pp. 350, with 93 illustrations. Elsevier Press, Inc., 402 Lovett Blvd., Houston 6, Texas, 1954.

The text is opened by a chapter on "Anatomical and Physiological Observations" in which the site and mode of formation of the cerebrospinal fluid are considered. It is heartening to read a genuine discussion of the still-disputed mode of prolongation of the cerebral blood vessels into the brain substance, the intimate anatomy of perivascular spaces, and the still-disputed perineuronal space. The scrutiny of the last problem is particularly refreshing to the reviewer, since it has always seemed to him that the early work of Weed (1923) has been accepted with too little criticism—specifically, that the histological evidence for the perineuronal space was meager, Weed himself taking it from Mott, in the latter's Oliver Sharpey Lecture of 1910, who, in turn, obtained his evidence from Bevan Lewis (1889). Louis B. Flexner, in 1933, subjected this aspect to considerable analysis in his critique, but this seems to have gone unnoticed, for in every modern textbook in the neurologic sciences one can find figured the now famous Weed diagram of the Virchow-Robin spaces. It is only recently, within the year, that Woollam and Millen, of Cambridge University, have presented some excellent evidence to indicate that the perineuronal spaces might be only artifacts!

Verjaal's very simple diagrams to illustrate fundamental changes in CSF pressure and its modifying factors are well presented, with full explanatory material. Hopefully, the authors have also dealt a final death blow to the Ayala index, whose clinical value has yet to be demonstrated.

Another chapter deals with detailed directions as to indications and contraindications for and technical steps in lumbar, cisternal, and ventricular punctures.

Many determinations, such as those of calcium, phosphorus, lipids, and residual nitrogen and lactic acid, are placed in their proper perspective. A scheme is presented for a complete examination of the CSF, from alpha to omega. A special section, comprising about two-fifths of the text material, deals with a thorough consideration of the CSF findings in syphilis, bacterial and viral leptomeningitides, encephalitis, space-occupying lesions, vascular diseases, epilepsy, degenerative and demyelinating diseases, etc.

The last of the four text chapters presents details for laboratory procedures in the various tests and will be of interest only to those engaged in the actual conduct of a research or clinical laboratory.

The publishers have produced a very acceptable volume both for its easily legible type and good quality paper and for its bringing this venture to our attention.

d is for
distance

D is for Devereux Schools

A full score of Devereux Schools, under the nonprofit Devereux Foundation, epitomize the heartening distance between the Salpetriere and serotonin. Between "training" or "custodial care" and dynamic education, art therapy, and objective environmental structuring under psychotherapeutic direction.

Pioneers in special education for almost half a century, Devereux Schools look to you and your professional associates increasingly for guidance. For a truly multidisciplined approach is as essential to special education as it is to you, in clinical practice.

We invite you to evaluate these schools; or to write for detailed information to

JOHN M. BARCLAY
Director of Development
The Devereux Foundation
Devon, Pennsylvania

Devereux Schools

UNDER THE DEVEREUX FOUNDATION

HELENA T. DEVEREUX, *Director*

Professional Associate Directors

ROBERT L. BRIGDEN, Ph.D.
MICHAEL B. DUNN, Ph.D.
EDWARD L. FRENCH, Ph.D.
ROBERT T. GRATTAN, M.D.
J. CLIFFORD SCOTT, M.D.

Santa Barbara, California

Devon, Pennsylvania

THORAZINE*

helps to keep more patients out of mental hospitals

With 'Thorazine' "more patients will be released after shorter periods of hospitalization and fewer patients will require re-hospitalization. More patients can be treated in the community, at clinics or in the psychiatrist's office without being hospitalized at all."[1]

'Thorazine' should be administered discriminately; and, before prescribing, the physician should be fully conversant with the available literature.

For information write: *Smith, Kline & French Laboratories, 1530 Spring Garden Street, Phila. 1*

1. Hoffman, J.L.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.